



MEDICINE

Third Edition

Dr. Irfan Masood (DMC) - Dr. Wida Elyassi - Dr. Waqas Rind (DMC)



Dr. Irfan Masood



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PREFACE

THIS BOOK IS DEDICATED TO

Dr. Ahmed Jawid Elyassi & his wife Dr. Atifa Elyassi

(Who Always Walk in When Others Walk Out)

My Parents & Siblings

(My Immunity)

Rida Irfan

(For Her Unconditional Love & Support)



To My Kids

(Wali & Nida)

PREFACE

I am thankful to Almighty God who gave me the courage to write the second edition of this book, with great support from my co-authors Dr. Wida Elyassi and Dr. Waqas Rind. This concise review of medicine is designed for undergraduate medical students as well as others in the health care professions.

This book presents condensed and succinct descriptions of relevant and current information pertaining to internal medicine without the usual associated details.

The objective is to give students a precise text that extensively covers the subject matter and the examination need (MCCQs & VIVA). **Extreme care has been taken to confirm the accuracy of the information presented & to describe the generally accepted practices.** This book is for revision only and is not meant to be a substitute for the comprehensive presentation of information and difficult concepts found in standard medicine texts. Application of the information in a particular situation remains the professional responsibility of the practitioner, for which the authors, editors, and publishers are not responsible.

I welcome comments, suggestions, and constructive criticism of this book, which may be addressed at dr_irfan15@hotmail.com

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ABBREVIATIONS

ACA	=	anterior cerebral artery	IBD	=	inflammatory bowel disease
ACTH	=	adrenocorticotrophic hormone	IFN	=	interferon
ADH	=	anti-diuretic hormone	IGF-1	=	insulin-like growth factor 1
AIDS	=	acquired immunodeficiency syndrome	IL-1	=	interleukin 1
ALT	=	alanine transaminase	IL-6	=	interleukin 6
AMA	=	anti-mitochondrial antibody	IM	=	intramuscular
ANA	=	anti-neutrophilic antibody	IV	=	intravenous
Anti-CCP	=	anti-citrullinated peptide	IVIG	=	intravenous immunoglobulin
APTT	=	activated partial thromboplastin time	LH	=	luteinizing hormone
ASO	=	anti-streptolysin-O	MCA	=	middle cerebral artery
AST	=	aspartate transaminase	MCP	=	metacarpophalangeal joint
BBB	=	blood brain barrier.	MRCp	=	magnetic resonance cholangiopancreatography
BP	=	blood pressure	MTP	=	metatarsophalangeal joint
BT	=	bleeding time	NDI	=	nephrogenic diabetes insipidus
cAMP	=	cyclic adenosine monophosphate	OA	=	osteoarthritis
CBC	=	complete blood count	PAS	=	periodic-acid Schiff
CD	=	Crohn's disease	PBC	=	primary biliary cirrhosis
CDI	=	central diabetes Insipidus	PIP	=	proximal interphalangeal joint
CEA	=	carcinoembryonic antigen	PMR	=	polymyalgia rheumatica
CNS	=	central nervous system	PNS	=	peripheral nervous system
COPD	=	chronic obstructive pulmonary disease	PSC	=	primary sclerosing cholangitis
CPK	=	creatinine phosphokinase	PT	=	prothrombin time
CRP	=	C-reactive protein	PTH	=	parathyroid hormone
CSF	=	cerebrospinal fluid	PTHrP	=	parathyroid hormone related peptide
DI	=	diabetes insipidus	RA	=	rheumatoid arthritis
DIP	=	distal interphalangeal joint	RANK	=	receptor activator for nuclear factor kB.
DM	=	diabetes mellitus	RANKL	=	RANK-ligand
ERCP	=	endoscopic retrograde cholangiopancreatography	RF	=	rheumatoid factor
ESR	=	erythrocyte sedimentation rate	RIF	=	right iliac fossa
FSH	=	follicle stimulating hormone	RUQ	=	right upper quadrant
GGT	=	gamma glutamyltransferase	SAAG	=	serum albumin-ascites gradient
GH	=	growth hormone	SIADH	=	syndrome of inappropriate ADH secretion.
GHRH	=	growth hormone releasing hormone	SLE	=	systemic lupus erythematosus
GnRH	=	gonadotropin releasing hormone	TIPSS	=	Trans-jugular intra-hepatic portosystemic shunt
HIV	=	human immunodeficiency virus	TNF	=	tumor necrosis factor
HLA	=	human leukocyte antigen	TSH	=	thyroid stimulating hormone
HPV	=	human papillomavirus	UC	=	ulcerative colitis
HTN	=	hypertension	UCE	=	urea, creatinine, electrolyte

Chapter 1

POISONING



Initial Management of Poisoning:

I. Gastrointestinal Decontamination:

▪ Activated Charcoal:

- It absorbs toxins in the bowel as a result of its large surface area.
- It therefore, prevents absorption of significant proportion of ingested toxin.
- Its efficacy decreases with time, and in most cases it should be given within 1 hour.
- Dosing:
 - Single dose is recommended within 1 hour for substances ABSORBED by activated charcoal.
 - Multiple dose is recommended for serious poisoning, irrespective of time of presentation:
 - Carbamazepine
 - Phenobarbital
 - Dapsone
 - Quinine
 - Theophylline

○ Poorly Absorbed Substances:

- Iron
- Lithium
- Chemicals:
 - Acids
 - Alkalis
 - Ethanol
 - Ethylene glycol

- Methanol
- Mercury
- Petroleum distillates

▪ **Gastric Aspiration & Lavage:**

- It should not be employed routinely in acute poisoning.
- It is not more effective than activated charcoal.
- It is associated with more complications – mostly importantly aspiration.
- It can be used for substances that are poorly absorbed by activated charcoal (see above).
- It is, however, contraindicated in poisoning due to:
 - Acids
 - Alkalis
 - Petroleum distillates

▪ **Whole Bowel Irrigation:**

- Method:
 - It involves administration of large amount of osmotically balanced polyethylene glycol & electrolyte solution – usually by NG tube.
- Indications:
 - Poisoning with sustained-release or emetic-coated drugs.
 - Poisoning with iron
 - Poisoning with lithium
 - Ingested packets of illicit drugs.
- Contraindications:
 - Inadequate airway protection – risk of aspiration
 - Hemodynamic instability
 - Gastrointestinal hemorrhage
 - Bowel obstruction
 - Ileus

II. Urinary Alkalinization:

- Remember:

(Like for Like = Reabsorption)

 - Basic substances will be reabsorbed from urine if urinary pH is basic.
 - Acidic substances will be reabsorbed from urine if urinary pH is acidic.

- Therefore, in order to facilitate urinary excretion of acidic substances, urine pH should be alkalized (pH > 7.5).
- This is because, at basic pH, acidic substances will be highly ionized that pass poorly through lipid membranes, resulting in enhanced urinary excretion.
- It is achieved by administration of sodium bicarbonate.
- Indications:
 - Salicylate poisoning
 - Methotrexate poisoning

III. Hemodialysis & Hemoperfusion:

- **Introduction:**
 - These can enhance the elimination of poisons with:
 - Small volume of distribution
 - Long half-life after overdose
 - Hemodialysis – it is used when toxins are small enough to cross the dialysis membrane.
 - Hemo-perfusion – it involves binding of toxins to activated charcoal.
- **Indications:**
 - Hemodialysis:
 - Ethylene glycol
 - Methanol
 - Salicylates
 - Lithium
 - Sodium valproate
 - Isopropanol
 - Hemo-perfusion:
 - Theophylline
 - Phenytoin
 - Carbamazepine
 - Phenobarbital
 - Amobarbital

IV. Lipid Emulsion Therapy:

- It is used for poisoning with lipid-soluble agents.
- It is thought that lipid-soluble toxins partition into the IV lipid, reducing target tissue concentration.
- **Dosing:**
 - It involves administration of IV 20% lipid emulsion.
 - 1.5 mL/kg, followed by continuous infusion of 0.25 mL/kg/min until there is clinical improvement.
- **Indications:**
 - Local anesthetics
 - Tricyclic antidepressants
 - Calcium channel blockers
 - Lipid-soluble beta-blockers – e.g. propranolol

Poisoning by Specific Pharmaceutical Agents:

I. Paracetamol (Acetaminophen):

▪ **Clinical Features:**

- Initially: nausea, vomiting and right upper quadrant pain.
- Later (> 24 hours): liver failure (jaundice & encephalopathy) ± renal failure.

R_x

Management:

- Gastric lavage if > 12g (or > 150mg/kg) taken within 1 hour.
- Activated charcoal can be used in patients presenting within 1 hour.
- **Intravenous N-acetylcysteine (NAC) is the antidote of choice.**
- NAC acts by replenishing the hepatic glutathione.
- NAC provides complete protection against toxicity if given < 10 hours after overdose.
- If < 8 hours since overdose and plasma paracetamol is above normal limit, start NAC.
- If > 8 hours and suspicion of large overdose (> 7.5 g), start NAC, which can be stopped later if plasma level is below treatment line and INR/ALT are normal.
- Staggered Overdose:
 - It refers to multiple ingestion of paracetamol over several hours or days.
 - In such cases plasma paracetamol level will be un-interpretable.
 - In such cases NAC should be given if paracetamol dose exceeds 150 mg/kg bodyweight in any one 24-hour period.
- Regimen for NAC:
 - 150mg/kg in 200 ml 5% dextrose water over 15 minutes.
 - Then 50 mg/kg in 500 ml 5% dextrose water over the next 4 hours.
 - Then 100 mg/kg in 1000 ml 5% dextrose water over the ensuing 16 hours.
 - Total dose = 300 mg/kg over 20.25 hours.
- Side-effects of NAC:
 - Anaphylactoid Reaction (due to histamine release):
 - Mild = itching and urticaria
 - Severe = bronchospasm and hypotension
 - Rx = temporary stop NAC & give anti-histamine
- Alternative Antidote:
 - Methionine – 2.5g orally 4-hourly to a total of 4 doses.
 - Less effective than NAC.

II. Salicylate (Aspirin) Poisoning:

Clinical Features:

- Mild (> 150 mg/kg bodyweight)
 - Nausea and vomiting
 - Tinnitus and deafness
 - Hyperventilation and **"Respiratory Alkalosis"**
- Moderate (> 250 mg/kg bodyweight)
 - Peripheral vasodilation
 - Bounding pulses and profuse sweating.
- Severe (> 500 mg/kg bodyweight):
 - **"Metabolic acidosis"**
 - Hyperglycemia
 - Hyperpyrexia
 - Hypo-prothrombinemia
 - Renal failure
 - Pulmonary edema
 - Shock and cerebral edema

RX

Management:

- Activated charcoal to block absorption if patient presents within 1 hour.
- Intravenous sodium bicarbonate to correct acidosis.
- **"Urinary Alkalinization"**:
 - It is indicated when aspirin level is > 500 mg/L (600-800 mg/L).
 - **It increases the rate of aspirin excretion.**
 - It is done with dextrose water plus **"sodium bicarbonate"**.
- Hemodialysis (indicated when):
 - Serum aspirin level is > 700 mg/L.
 - Refractory metabolic acidosis
 - Renal failure
 - Pulmonary edema
 - Coma and convulsions

III. Tricyclic Antidepressants (TCA):

- TCA overdose is associated with high morbidity and mortality relating to their sodium channel-blocking, anti-cholinergic and α -blocking effects.

▪ **Clinical Features:**

- Tachycardia, hypertension
- Confusion, hallucination
- Dilated pupils
- Dry mouth, hot and dry skin
- Urinary retention
- Constipation
- Increased reflexes and extensor plantar responses
- Severe Intoxication(**Mnemonic: 3 C's**):
 - Coma
 - Convulsions& divergent strabismus
 - Cardiac – ECG = prolongation of QRS interval – risk of arrhythmia

R_x

Management:

- Perform 12-lead ECG and cardiac monitoring for at least 6 hours.
- **IV "Sodium Bicarbonate":**
 - It will protect the heart against arrhythmia.
 - **Unlike for aspirin toxicity, bicarbonate does NOT increase urinary excretion of TCAs.**
 - Indications:
 - Arrhythmias
 - Severe ECG effects
 - Acidosis
- Adequate oxygenation
- Intravenous benzodiazepines for prolonged convulsions.
- Lipid emulsion therapy in severe intractable poisoning.

IV. Lithium:

- Lithium toxicity is usually the result of therapeutic overdosage (chronic toxicity) rather than deliberate self-poisoning (acute toxicity).
- **Clinical Features:**
 - Polyuria, thirst, diarrhea, and vomiting.
 - Dizziness and tremor
 - Muscular weakness, myoclonus, fasciculations, choreoathetosis
 - Severe poisoning:
 - Coma, convulsions, and ataxia
 - Cardiac arrhythmias, blood pressure disturbances
 - Renal failure

R_x

Management:

- Forced diuresis with sodium chloride 0.9% is effective in elimination of lithium.
- **Dialysis is the treatment of choice** and is indicated when:
 - Lithium concentration > 4 mmol/L after chronic poisoning.
 - Lithium concentration > 7.5 mmol/L after acute poisoning.
 - If neurologic features are present.
 - If renal function is impaired.

V. Iron:

▪ Clinical Features:

- GI disturbance with passage of grey or black stools.
- Hematemesis or rectal bleeding.
- Hyperglycemia and leukocytosis.
- Severe poisoning:
 - Drowsiness, convulsions, coma
 - Metabolic acidosis and cardiovascular collapse

R_x

Management:

- Gastric lavage – within 1 hour of overdose.
- Activated charcoal is ineffective since iron is not bound.
- Treatment is supportive and directed at complications.
- **The antidote of choice is desferrioxamine**, which chelates iron.
- Desferrioxamine should be given in patients with:
 - Features of severe poisoning
 - Symptomatic patients with high serum iron concentration (e.g. > 5 mg/L)

Drugs of Misuse:**I. Cannabis (Marijuana):****▪ Clinical Features:**

- Low doses:
 - Euphoria, **perceptual alterations, and conjunctival injection**
 - Followed by relaxation, drowsiness, HTN, tachycardia, slurred speech and ataxia
- High doses:
 - Anxiety, confusion, hallucinations
 - Psychosis

R_x**Management:**

- Smoking or ingestion of cannabis rarely results in serious poisoning.
- Supportive treatment is all that is required.

II. Benzodiazepines:

- BDZs are sedative hypnotics.
- BDZs are of low-toxicity when taken alone in overdose, but can enhance CNS depression when taken with other sedative agents & alcohol.
- **Clinical Features:**
 - Rapid onset weakness, ataxia, drowsiness
 - Eyes – diplopia, nystagmus
 - Respiratory depression – decreased respiratory rate & ventilation
 - CNS depression – sedation, confusion, coma
 - Pupil size – normal

R_x**Management:**

- Patients should be observed for ≥ 6 hours post-ingestion
- Activated charcoal, if presented within 1 hour of ingestion.
- With particular attention to maintenance of airway in those with impaired consciousness.
- **Flumazenil is specific benzodiazepine antagonist.**
- Flumazenil is however contraindicated in (as it may cause convulsions):
 - Mixed TCA + Benzodiazepine poisoning.
 - Those with history of seizures

III. Cocaine:

- Cocaine is a stimulant by acting as sympathomimetic amines.
- **Clinical Features:**
 - Respiratory – tachypnea
 - CVS – tachycardia, HTN
 - CNS – anxiety, insomnia, and hallucinations
 - Muscle – tremors
 - Eyes – **dilated pupils**
 - Others – fever, abdominal pain, diarrhea, dry mouth, and pilo-erection
 - Complications:
 - Myocardial infarction (coronary artery spasm)
 - Rhabdomyolysis
 - Renal failure
 - Intracerebral hemorrhage

R_x

Management:

- Observation with ECG monitoring for a minimum of 4 hours.
- “**Benzodiazepine**” + aspirin + nitrates for chest pain and hypertension.
- IV diazepam for agitation and convulsions.
- Active external cooling for hyperthermia
- **Beta blockers are contraindicated for treatment of HTN, as they may cause paradoxical HTN (from unopposed alpha-adrenoceptor stimulation)**

IV. Opioids:

- Opioids include heroin, morphine, pethidine, codeine, methadone, and oxycodone.
- **Clinical Features:**
 - Respiratory depression
 - CVS – hypotension and relative bradycardia
 - CNS – confusions, hallucinations, slurred speech
 - Muscle – ataxia and reduced muscle tone
 - **Pinpoint pupils**
 - Signs of IV drug misuse (e.g. needle track marks)

R_x

Management:

- Airway should be cleared.
- Respiratory support and oxygen should be given, if necessary.
- **Intravenous naloxone (0.8 – 2 mg) is the specific opioid antagonist.**
- IV naloxone will reverse severe respiratory depression and coma at least partially.
- Non-cardiogenic pulmonary edema:
 - It does not usually respond to diuretic therapy.
 - It should be treated with mechanical ventilation:
 - Continuous positive airway pressure (CPAP)
 - Positive end-expiratory pressure (PEEP)

Chemicals, Pesticides, & Envenoming:

Chemicals & Pesticides:

I. Carbon Monoxide (CO):

- CO causes toxicity by binding with hemoglobin forming carboxy-hemoglobin (COHb), which reduces tissue oxygen delivery and inhibits cellular respiration.
- Clinical Features:
 - Initially: nausea, vomiting, ataxia, nystagmus, drowsiness, hyperventilation, hyper-reflexia, and shivering.
 - Later: coma, convulsions, hypotension, respiratory depression, and cardiovascular collapse, and ECG abnormalities, such as:
 - ST-depression; T-wave abnormalities
 - Ventricular tachycardia; ventricular fibrillation
 - Poisoning during pregnancy:
 - Fetal hypoxia
 - Intrauterine death

R_x

Management:

- Remove patient from source of exposure as soon as possible.
- **High-flow (100%) oxygen by tightly fitting facemask.**
- High-flow oxygen should be continued until COHb is < 5% and for at least 6 hours after exposure
- Endotracheal intubation and mechanical ventilation in unconscious patients.
- Hyperbaric oxygen can reduce the half-life of COHb:
 - At 2.5 atmospheres it reduces the half-life of COHb to about 20 minutes.
 - Its use is controversial – trials have failed to show clinical improvement

II. Ethylene Glycol:

- It is found in anti-freeze, car brake fluids, and windscreen washes.
- It is converted by alcohol dehydrogenase into toxic metabolites such as glycolic acid, glyoxylic acid, and oxalic acid.
- Clinical Features:
 - Ataxia, drowsiness
 - Dysarthria, nystagmus

- Increased anion gap metabolic acidosis
- Increased serum osmolality
- **Hypocalcemia** (from precipitation of oxalic acid with calcium)
- **Calcium oxalate crystals in urine**
- Hypomagnesemia, hyperkalemia
- Renal failure

R_x

Management:

- Intravenous ethanol, or fomepizole (both inhibits alcohol dehydrogenase)
- Sodium bicarbonate for metabolic acidosis
- Intravenous benzodiazepine for convulsions
- Dialysis if there is renal failure.

III. Methanol Poisoning:

- It is found in anti-freeze, industrial solvents, and screen washes.
- It is converted by alcohol dehydrogenase into toxic metabolite i.e. formic acid.
- **Clinical Features:**
 - Ataxia, drowsiness
 - Dysarthria, nystagmus
 - Increased anion gap metabolic acidosis
 - Increased serum osmolality
 - Visual impairment and photophobia
 - **Optic disc and retinal edema**
 - **Impaired pupil reflexes and blindness**

R_x

Management:

- Intravenous ethanol, or fomepizole (both inhibits alcohol dehydrogenase)
- Sodium bicarbonate for metabolic acidosis
- Intravenous benzodiazepine for convulsions
- Dialysis if there is renal failure or there is visual loss.

IV. Organophosphorus (OP) Poisoning:

- OP compounds are widely used as pesticides.
- OP compounds inactivate acetylcholinesterase (AChE) by phosphorylation, leading to accumulation of acetylcholine at cholinergic synapses.

▪ **Acute Cholinergic Syndrome:**

○ **Clinical Features:**

- It occurs within 1 hour of exposure and lasts 48 – 72 hours.
- Both muscarinic & nicotinic features occur in OP poisoning.
- Typical features – miosis and muscle fasciculations
- Respiratory - bronchoconstriction, bronchorrhea,
- CVS:
 - Cholinergic muscarinic – hypotension, bradycardia
 - Cholinergic nicotinic – hypertension, tachycardia
- CNS – confusion, seizures
- Muscle – fasciculation, paralysis
- Abdomen:
 - Cholinergic muscarinic – ileus, palpable bladder (urinary retention)
 - Cholinergic nicotinic – vomiting, profuse diarrhea
- Skin:
 - Cholinergic muscarinic – flushing, hot, dry
 - Cholinergic nicotinic – sweating
- Eye:
 - Cholinergic muscarinic – diplopia, mydriasis
 - Cholinergic nicotinic – lacrimation, miosis
- Complications:
 - Generalized flaccid paralysis – can affect respiratory and ocular muscles.
 - Torsades de pointes
 - Pancreatitis
 - Hepatic dysfunction
 - Pyrexia

R_x

Management:

- Remove contaminated clothing; wash skin with soap and water.
- Airway should be cleared; high-flow oxygen should be administered.
- Gastric lavage and activated charcoal only if within 1 hour of ingestion.
- Atropine:
 - It reverses acetylcholine-induced bronchospasm, bronchorrhoea, bradycardia and hypotension.
 - It should be administered in doses of 0.6 – 2 mg IV repeated every 10–25 minutes until secretions are controlled, the skin is dry, and there is a sinus tachycardia.
- Pralidoxime:
 - It reactivates phosphorylated acetylcholinesterase (AChE).
 - It reverses or prevents muscle weakness, convulsions, and coma.
 - It is given in doses of 2 g IV over 4 mins, repeated 4 – 6 hourly.

▪ Intermediate Syndrome:

- It occurs in 20% of patients with OP poisoning.
- It develops rapidly between 1 – 4 days after exposure.
- It often develops after resolution of acute cholinergic syndrome.
- It may last 2 – 3 weeks.

○ Clinical Features:

- Progressive muscle weakness (ocular, limbs and respiratory muscles)
- Respiratory failure

○ Management:

- No specific treatment
- Supportive care, including maintenance of airway and ventilation.

▪ OP-induced Delayed Polyneuropathy (OPIDN):

- It occurs 2 – 3 weeks after acute exposure or following chronic exposure.
- It is a mixed sensory and motor polyneuropathy due to degeneration of long myelinated nerve fibers.

○ **Clinical Features:**

- Muscle cramps, followed by numbness and paraesthesias.
- Ascending Paralysis:
 - Flaccid paralysis of lower limbs first, followed by upper limbs.
 - Paralysis of upper limbs is associated with wrist drop.
 - Paralysis of lower limbs is associated with foot drop, high-stepping gait & paraplegia.

○ **Management:**

- No specific treatment.
- Physiotherapy may limit deformity.
- Recovery is incomplete – often limited to the hands & feet.
- Functional recovery is better in younger patients.

Envenoming:

I. Introduction:

- It occurs when a venomous animal injects sufficient venom into a prey to cause deleterious local & systemic side-effects.

▪ **Clinical Features:**

○ **Local Effects:**

- Pain,
- Swelling, redness (erythema)
- Bleeding, bruising, blistering,
- Necrosis

○ **Non-Specific Systemic Effects:**

- Headache,
- Nausea, vomiting, diarrhea,
- Abdominal pain
- Hypertension, hypotension
- Tachycardia, bradycardia
- Dizziness, seizures
- Shock, cardiac arrest

○ **Specific Systemic Effects:**

(i). Neurotoxic Flaccid Paralysis:

- Rapid onset progressing to respiratory failure in < 30 minutes – blue ringed octopus bite, cone shell sting.
- Gradual onset of paralysis (over hours) – snakes
- Gradual onset of paralysis (over days) – tick paralysis

- Neurotoxic Snakes:
 - Affect cranial nerves first – usually presenting with ptosis.
 - Paralysis of limbs, loss of deep tendon reflexes, & respiratory paralysis.

(ii). Excitatory Neurotoxins:

- It presents with profuse sweating, variable cardiac effects, cardiac failure, & pulmonary edema.
- This can occur rapidly – scorpion bite, funnel-bite spider bite
- This can occur gradually – widow spider, banana spider

(iii). Myotoxicity:

- It presents with:
 - Generalized muscle pain & tenderness
 - Myoglobinuria, markedly elevated serum creatine kinase (CK)

(iv). Coagulopathy & Renal Failure:

- Bruising and bleeding from bite site, gums & IV sites.
- Thrombosis – DVT, PE, stroke.
- Renal failure is mostly secondary.
- Russell's viper can cause primary renal damage.

II. Management:

- **First Aid:**
 - Pre-hospital first aid is critical in management of envenoming.
 - It depends on the type of envenoming, but key principles are:

First Aid Envenoming

Immobilization of bitten limb	All snakebites
Pressure bandage + Immobilization of bitten limb	All necrotic snakebites
Local heat (hot water immersion to 45°C)	Venomous fish stings, stingray injuries, jellyfish
Cardiorespiratory Support	Cardiorespiratory Impairment (snakes, paralytic tics, blue-ringed octopus, cone shells)
No specific first aid	Widow & recluse spider bites



Clinical Pearl:

Harmful Treatments in Snakebites:

- Electric shock
- Cut & suck
- Tourniquets
- Cryotherapy

▪ Anti-Venom:

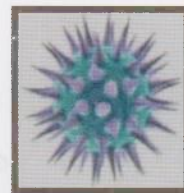
- It is the most important tool in treating envenoming.
- It is made by hyper-immuning horse, to produce antibodies against venom.
- Once refined, these bind to venom toxins & render them inactive, or allow their rapid clearance.
- Features:
 - It should be given intravenously – few exceptions.
 - IV adrenaline should be ready in case of anaphylaxis to anti-venom.
 - Doses vary widely between anti-venoms.
 - It can reverse POST-synaptic neurotoxic paralysis, but usually cannot reverse established PRE-synaptic paralysis.
 - It should therefore be given before major paralysis has occurred.
 - Coagulopathy is best reversed by anti-venom – variable rate
 - Its role in reversing established myolysis & renal failure is uncertain.

▪ Adjunct Treatments:

- Anti-cholinesterases – post-synaptic paralysis
- Alpha blocker (prazosin) – HTN & pulmonary edema of scorpion sting cardiotoxicity.
- Antibiotics – wound infection, abscess
- Tetanus toxoid – decreases risk of tetanus (IM toxoid should not be given until any coagulopathy is reversed).
- Mechanical ventilation – for established refractory respiratory paralysis.

Chapter 2

INFECTIOUS DISEASES



Viral Infections with Exanthem

- It is a group of systemic viral infections associated with exanthem.
- Exanthem refers to a wide-spread rash associated with fever in childhood.
- Enanthem refer to rash on mucous membranes.
- Maternal antibody gives protection for the first 6 – 12 months of life and infection occurs thereafter.
- Viral infections with exanthem are:
 - Measles (also has enanthem)
 - Rubella (also has enanthem)
 - Parvovirus B19
 - Human herpes virus 6 & 7
 - Chickenpox and Shingles

I. Measles:

- Introduction:
 - Agent = RNA paramyxovirus.
 - Incubation period = 6 – 19 days.
 - Mode of transmission = respiratory droplets.
- Clinical Features:
 - Prodrome of 1 – 3 days. (mnemonic: harsh "C" sounds)
 - Cough
 - Coryza (runny nose)
 - Conjunctivitis
 - Enanthem: **Koplik's spots:**



- These are small, white spots surrounded by erythema on buccal mucosa.
- These are pathognomonic of measles.
- Exanthem:
 - Maculopapular rash, starts at head and spreads downwards.
 - Rash fades in the same manner (i.e. from head downwards).
- **Complications:**
 - Otitis media – most common
 - Pneumonia
 - Encephalitis – most feared complication
 - Subacute sclerosing panencephalitis (SSPE) – a rare late complication
 - **Measles does NOT cause congenital abnormalities.**

R_x

Management:

- Supportive
- Vitamin A
- Normal Human Immunoglobulin:
 - **It is given within 6 days of exposure.**
 - It effectively aborts an attack of measles.
 - It is indicated in:
 - Immunocompromised individuals
 - Non-immune pregnant women
 - Non-immune children < 3 years of age.
- Prevention:
 - Vaccination at 12 – 15 months after birth.
 - Vaccine is a live, attenuated vaccine, given as combined measles, mumps, rubella (MMR).

II. Rubella:

- **Introduction:**
 - Also known as “German Measles”, or “3 day Measles”.
 - Agent = RNA virus (togavirus)
 - Incubation period = 15 – 20 days
 - Mode of transmission = respiratory droplet
 - Infectivity period = 10 days before to 2 weeks after the onset of rash.

▪ **Clinical Features:**

- Prodromal illness:
 - Fever, malaise, lymphadenopathy.
 - **Lymphadenopathy is characteristic** and involves sub-occipital, post-auricular, and posterior cervical groups of lymph nodes.
 - Enanthem = **Forchheimer Spots:**
 - These are small petechial lesions on the soft palate.
 - These are suggestive, but not diagnostic of rubella.
- Exanthem:
 - Maculopapular rash (similar to measles).
 - Begins on face and spreads to the rest of body, lasts approximately 3 days.

▪ **Complications:**

- Thrombocytopenia
- Hepatitis,
- Encephalitis
- Congenital Infections:
 - Risk of congenital infections is highest if infection occurs in 1st trimester.
 - **Congenital Rubella Syndrome:**
 - Congenital deafness
 - Congenital cataract
 - Congenital heart disease (patent ductus arteriosus)
 - Mental retardation

R_x

Management:

- Diagnosis:
 - Rubella-specific IgM by ELISA – acute infection
 - IgG Seroconversion (14 days after acute infection)
- Prevention:
 - MMR (as for measles)
 - All women of child-bearing age should be tested for rubella and vaccinated if seronegative.
 - Treatment is supportive.

III. Erythema Infectiosum (Fifth Disease):

■ Introduction:

- Agent = Parvovirus B19
- Incubation period = 14 – 21 days.

■ Clinical Features:

- Prodromal illness:
 - Fever and coryzal symptoms.
 - No enanthem.
- Exanthem:
 - **"Slapped Cheek Syndrome"**, which is intensely red rash on the face.
 - Followed by lacy, reticular rash over trunk and extremities sparing palms and soles.

■ Complications of Parvovirus B19:

- Gloves & Socks syndrome = purpuric rash with a clear margin at the wrists and ankles.
- Arthropathies = more common in adults, symmetrical, small joint polyarthritis.
- Impaired Erythropoiesis:
 - It results in **"aplastic crisis"** in those with underlying hematologic abnormality
 - Erythropoiesis, however recovers spontaneously after 10 – 14 days.
- Hydrops Fetalis:
 - It occurs during transplacental fetal infection.
 - It is a non – immune (non-Rhesus related) Hydrops Fetalis (erythroblastosis fetalis)

R_x

Treatment:

- Supportive.
- Pregnant women:
 - Pregnant women should avoid contact with cases of parvovirus B19 infection.
 - If they are exposed, perform serology to know the immune status.
 - Pregnancy should be closely monitored by ultrasound.
 - Fetal transfusion, if hydrops fetalis is detected

IV. Exanthem Sabinum (Sixth Disease):

Introduction:

- Also known as = Roseola
- **Agent = human herpes virus 6 & 7 (HHV-6 and HHV-7)**
- Mode of transmission = saliva
- Target = infects CD4 T-cells

Clinical Features:

- High-grade fever up to 106°F, which resolves by the 3rd or 4th day.
- Followed by a maculopapular rash (rose-colored) on the trunk, arms, neck, and face.
- In older patients it may present with infectious mononucleosis-like syndrome.
- Complications:
 - Febrile convulsions
 - Aseptic meningitis
 - Encephalitis
 - Pneumonia

Treatment:

- Supportive
- Gancyclovir in immunocompromised infected with HHV-6.

V. Varicella Zoster Virus (VZV) Infection:

- VZV is a herpes virus (DNA enveloped virus)
- VZV produces two distinct diseases:
 - Primary infection = Chickenpox (varicella)
 - Reactivation infection = Shingles (herpes zoster)

(i). Chickenpox:

Introduction:

- Mode of transmission = respiratory secretion
- Incubation period = 11 – 20 days.
- Infectivity period = 4 days before the rash appears until the last vesicles crust over.

▪ **Clinical Features:**

- Tear-drop vesicular rash in a “**centripetal distribution**” i.e. more on trunk than on limbs.
- Pruritic (intensely itchy) rash is in various stages i.e. progresses from small pink macules, to vesicles and pustules within 24 hours.
- New crop (lesions) occurs every 2 – 4 days and each crop is associated with fever.

▪ **Complications:**

- Secondary bacterial infection from scratching – most common
- Pneumonia
- Hepatitis
- Encephalitis
- **Pregnancy:**
 - Maternal infection in early pregnancy causes developmental abnormalities of eye, CNS, and limbs.
 - Maternal infection within 5 days of delivery leads to severe neonatal varicella with visceral involvement and hemorrhage.

R_x

Management:

○ **Antivirals Agents (Indications):**

- Uncomplicated chickenpox – (presenting within 24 – 48 hr onset of vesicles)
- Complicated chickenpox – regardless of duration of vesicles
- Immunocompromised hosts – regardless of duration of vesicles
- Pregnant women – regardless of duration of vesicles
- Oral Antivirals:
 - Agents – acyclovir (800 mg x 5 times/day), famciclovir (500mg x 3/day).
 - It is given for 5 days.
 - Indications – adults, immunocompetent, and children
- IV Antivirals:
 - Indications – immunocompromised host, pregnant women
 - IV antivirals until patient is improving, then switch to oral form until all lesions crust over.

○ **Varicella Zoster Immunoglobulin (VZIG):**

- It is ideally given within 7 days of exposure (not infection).
- It may attenuate disease even if given up to 10 days afterwards.
- It is indicated in following conditions:
 - Those with significant contact e.g.:
 - Sharing a room for > 15 minutes
 - Face-to-face contact.
 - Intimate contact with person with shingles
 - Hospital contact with chickenpox (patient, visitor, healthcare worker).
 - Susceptible host (i.e. individuals with no history chickenpox)
 - Pregnant women (at any stage)
 - Immunocompromised individuals:
 - Acute leukemia, HIV,
 - Organ transplantation, high-dose steroids
 - Newborns:
 - Premature infants < 28 weeks.
 - **Newborn whose mother develops chickenpox within 5 days before or 2 days after delivery.**
- Prevention:
 - VZV vaccine is a live attenuated vaccine.
 - Children receive 1 dose after 1 year of age and a second dose at 4-6 years of age.
 - Adults receive 2 doses at least 1 month apart.

(ii). Shingles (Herpes Zoster):

▪ **Introduction:**

- VZV after primary infection becomes dormant in dorsal root ganglion of sensory nerves.
- VZV when reactivated later in life causes shingles.

▪ **Clinical Features:**

- It is more common in elderly.
- It presents with rash that is classically unilateral and restricted to a sensory nerve (i.e. a dermatomal rash).

- The onset of rash is preceded by severe dermatomal pain.
- **The most common dermatomes are thoracic dermatomes.**
- The rash frequently involves the ophthalmic division of trigeminal nerve that may lead to corneal ulceration and blindness.
- **Ramsay Hunt Syndrome:**
 - It occurs when the virus involves geniculate ganglion.
 - It presents with facial palsy, ipsilateral loss of taste and buccal ulceration, plus vesicular rash in the external auditory canal.
- **Post-herpetic Neuralgia:**
 - It is the most common complication of shingles.
 - It refers to persistent pain for 1 – 6 months following healing of the rash.

R_x

Treatment:

- Early therapy with aciclovir.
 - It reduces both early and late-onset pain.
 - It is very effective in those > 65 years.
- Post-herpetic Neuralgia:
 - Aggressive analgesia
 - Amitriptyline or Gabapentin

Viral Infections without Exanthem

I. Mumps:

▪ Introduction:

- Agent = paramyxovirus
- Incubation period = 15 – 24 days.
- Infectivity period = 2 days before to 3 days after parotid swelling

▪ Clinical Features:

- It is primarily a disease of school-aged children
- The prodromal symptoms are non-specific (fever, malaise, and headache).
- This followed by tender parotid enlargement, which is bilateral in 75% of cases.
- Complications:
 - Epididymo-orchitis:
 - It occurs in 25% of post-pubertal males.
 - It causes testicular atrophy, but sterility is unlikely
 - **Meningo-encephalitis – most common complication**
 - Oophoritis
 - Pancreatitis
 - Abortion (if infection occurs during 1st trimester of pregnancy)
 - Myocarditis, hepatitis, polyarthritis

▪ Diagnosis:

- Clinical diagnosis
- Mumps specific IgM in acute infection

R_x

Management:

- Prevention is by vaccination (MMR).
- Treatment of acute infection:
 - Supportive
 - Treat orchitis with bed rest and local support
 - Steroids for arthritis

II. Infectious Mononucleosis:

Introduction:

- Agent = **Epstein-Barr Virus (EBV)**, a gamma herpes virus.
- Mode of transmission = saliva and aerosol (kissing disease)
- It is NOT highly contagious; therefore isolation of cases is not necessary.

Clinical Features:

- Fever, fatigue, pharyngitis.
- Cervical lymphadenopathy (posterior > anterior cervical nodes)
- Splenomegaly
- Hepatitis
- Antibiotic – induced rash (80 – 90% with ampicillin for sore-throat)

Complications:

- Airway obstruction – due to severe pharyngeal edema
- Splenic rupture
- Thrombocytopenia
- Neurologic (e.g. cranial nerve palsies)
- X-lined lymphoproliferative syndrome (Duncan's syndrome)
- EBV – associated Malignancy:
 - **Nasopharyngeal carcinoma**
 - **Burkitt's lymphoma**
 - Primary CNS lymphoma
 - Hodgkin's disease

Diagnosis:

- **Atypical lymphocytosis:**
 - These are activated CD8 T-lymphocytes.
 - They are also called "glandular fever cells".
 - These are non-specific findings.
- **"Heterophile antibodies"** – detected by Monospot Test.
- Acute Infection is characterized by:
 - **IgM to viral capsid antigen is the most valuable and specific.**
 - **IgM antibodies to EBV early antigen.**
 - **Initial absence of antibodies to EBV nuclear antigen (anti-EBNA)**

Rx

Treatment:

- It is largely supportive.
- Steroids for 5 days – if pharyngeal edema is severe
- Steroids can be given for neurologic involvement, thrombocytopenia, and hemolysis
- **Avoid contact sports or strenuous activity until splenomegaly has resolved – (risk of rupture)**

III. Dengue:

■ Introduction:

- Agent = dengue virus which is a flavivirus.
- There are 4 serotypes of dengue virus
- Principal vector is the mosquito "**Aedes aegypti**".
- It is the most common arthropod-borne viral infection in humans.
- Incubation period = 2 – 7 days following mosquito bite.
- Homotypic immunity after infection with one of the serotypes is life-long.
- Heterotypic immunity against the other serotypes lasts only a few months after infection.

■ Clinical Features:

- Prodromal illness of malaise and headache for 2 days.
- Followed by fever, arthralgias, and headache.
- "**Break-Bone Fever**" i.e. generalized pain, and pain on eye movements.
- Lacrimation, nausea, vomiting, relative bradycardia, and lymphadenopathy.
- **Tourniquet Test:**
 - Petechiae occur in the arm when BP cuff is inflated to a point between SBP & DBP and left for 5 minutes.
 - It is seen in mild forms, and indicate capillary fragility & thrombocytopenia – (non-specific test)
- Fever:
 - Continuous for 7 – 8 days, OR
 - "**Saddle-back**" fever, i.e. with a break on 4th or 5th day and then recrudescence
 - "**Critical Phase**":
 - It is the period 3 – 7 days after the onset of fever.

- It is during this period that signs of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) may develop.

- Rash:

- In first 1–2 days = faint macular rash
- From days 3–5 = **maculopapular, morbilliform rash that blanches on pressure**; spreading centrifugally and sparing palms and soles.

- **Dengue Hemorrhagic Fever (DHF):**

- It is a severe form of dengue fever.
- It is believed to be the result of two or more sequential infections with different dengue serotypes.
- Clinical Features:
 - Thrombocytopenia
 - Hemorrhage
 - Hypotension
 - Circulatory failure:
 - Pleural effusion
 - Ascites
 - Hypoalbuminemia
 - Acute respiratory distress syndrome (ARDS)

- **Diagnosis:**

- CBC = leukopenia and thrombocytopenia
- Confirmatory tests:
 - Fourfold rise in IgG antibody titres.
 - Detection of dengue virus RNA by PCR.

- **Management:**

- Treatment is symptomatic – no existing antivirals are effective.
- Aspirin should be avoided due to bleeding risk.
- Volume replacement and blood transfusions in patient with shock.
- Corticosteroids have not been shown to help.
- Preventions:
 - Breeding places of Aedes mosquito should be abolished.
 - Adult should be killed by insecticides.
 - There is no vaccine.

Bacterial Infections

I. Staphylococcal Infections:

(i). Scalded Skin Syndrome (SSSS):

- Also known as "Ritter's syndrome".
- It is a dermatological condition caused by toxin-secreting strain of *S. aureus*.
- Pathogenesis:
 - It is caused by production of toxin, "exfoliatin".
 - It causes intra-epidermal cleavage at the level of stratum corneum leading to formation of large flaccid blisters that shear readily.
- Clinical Features:
 - It affects children under the age of 5 years.
 - Thin-walled fluid filled blisters.
 - Sparing the mucous membrane (unlike toxic epidermal necrolysis and Stevens-Johnson syndrome, which involve mucous membranes)
- Treatment:
 - It is a relatively benign condition.
 - It responds to treatment with flucloxacillin.

(ii). Toxic Shock Syndrome (TSS):

- Causes:
 - Toxin-secreting staphylococcus aureus (most common)
 - Toxin-secreting streptococci
- Pathogenesis:
 - It is caused by exotoxin called "toxic shock syndrome toxin 1" (TSST-1).
 - It acts as super-antigen triggering significant CD4 (helper) T-cell activation with massive cytokine release.
- Clinical Features:
 - It is associated with vaginal colonization and tampon use in women.
 - Sudden onset of fever, myalgia, headache, sore-throat, and vomiting, and hypotension.
 - Generalized, erythematous blanching rash with desquamation of palms and soles.
 - Multi-system involvement with cardiac, renal, and hepatic compromise.
 - Mortality rate is 10–20%.

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Treatment:

- Immediate and aggressive fluid resuscitation.
- Antibiotics:
 - Intravenous flucloxacillin or vancomycin, PLUS
 - Clindamycin (protein synthesis inhibitor to inhibit toxin production)
- Intravenous immunoglobulin.
- Women who recover should be advised not to use tampons for at least 1 year.

II. Typhoid & Paratyphoid Fevers:

▪ Introduction:

- Also known as “**Enteric Fevers**”.
- Agent = salmonella typhi and salmonella paratyphi.
- Incubation period = 10 – 14 days.
- Mode of transmission = fecal – oral

▪ Clinical Features:

- **First Week:**
 - Fever, rising in a stepladder fashion for 4 – 5 days.
 - Malaise, headache, drowsiness and aching in the limbs.
 - Constipation;
 - Relative bradycardia (i.e. pulse is slow than would be expected from the height of temperature)
- **Second Week:**
 - Rose-spots (rose-colored rash on upper abdomen & back which fade on pressure)
 - Cough and epistaxis
 - Splenomegaly (7th – 10th day)
 - Constipation is then succeeded by diarrhea and abdominal distention with tenderness.
- **Third Week:**
 - Complications:

- Bowel perforation; hemorrhage
- Cholecystitis, myocarditis; nephritis
- Most common cause of osteomyelitis in patients with sickle cell disease
- **Chronic carrier state due to "gallbladder colonization"**

▪ **Diagnosis:**

- Blood culture = **most accurate test**
- Stool culture = **will contain organism during 2nd and 3rd week.**

R_x

Treatment:

- Drug of choice:
 - **Fluoroquinolones (ciprofloxacin 500mg 12-hourly) x 14 days.**
 - **Fever may persist for up to 5 days after the start of therapy.**
- Resistant cases = **Cephalosporins (ceftriaxone, cefotaxime), Azithromycin**
- Chronic carriers = **Ciprofloxacin for 4 weeks ± cholecystectomy.**

III. Clostridium difficile Infection:

- Clostridium difficile is a gram-positive rod.
- Clostridium difficile infection is most commonly caused by broad-spectrum antibiotic therapy.
- **Clinical Features:**
 - Symptoms usually begin the 1st week of antibiotic therapy (intravenous)
 - Lower abdominal pain, profuse watery diarrhea.
 - Raised WBC count
 - Pseudomembranous Colitis:
 - Above symptoms, PLUS:
 - Formation pseudomembrane on colon mucosa + bowel wall thickening.
 - Fulminant Colitis:
 - It presents in 2 – 3% of patients.
 - It presents with toxic megacolon (colon dilatation ≥ 6 cm on AXR), systemic toxicity ± bowel perforation.

▪ **Diagnosis:**

- Only test if symptomatic
- Detection of *C. difficile* toxin (toxin A or B) in:
 - Stool using ELISA
 - Stool PCR – quick, becoming test of choice.
- Alternative: 2-Step Method:
 - Step-1 : check glutamate dehydrogenase (GDH) by enzyme immunoassay (EIA)
 - Step-2 : if step-1 is positive, check cytotoxin assay.

R_x

Treatment:

- Stop the precipitating antibiotic and patient should be isolated.
- Supportive therapy with intravenous fluids and resting of the bowel is often needed.
- Mild – Moderate Infection:
 - Indications – WBC < 15000, Cr < 1.5 x baseline, age < 65, no peritoneal signs)
 - Agent – oral metronidazole (500 mg x 3/day) x 10 – 14 days.
- Severe Infection:
 - Indications – WBC > 15000, Cr > 1.5 x baseline, age > 65, peritoneal signs)
 - Agent: oral vancomycin x 10 – 14 days – OR – IV metronidazole
- Recurrent Infection:
 - 1st relapse = PO metronidazole – OR – PO vancomycin x 10 – 14 days
 - 2nd relapse = PO vancomycin (taper for 6 weeks)
 - > 2 relapses = Vancomycin taper + Adjuvant therapy (probiotics, Rifaximin, Nitazoxanide, “Fidaxomicin”)
 - Refractory = fecal transplant (appears safe & effective)

IV. Mycobacterial Infection:

Leprosy:

Introduction:

- Also known as “Hansen’s disease”.
- It is a chronic granulomatous disease affecting skin and nerves, caused by *Mycobacterium leprae*.
- *Mycobacterium leprae* is a slow-growing mycobacterium which cannot be cultured in vitro.
- Mode of transmission = nose
- It can have two presentations:
 - Tuberculoid Leprosy:
 - When cell-mediated immunity is high
 - Incubation period = 2–5 years
 - Lepromatous Leprosy:
 - When cell-mediated immunity is absent.
 - Incubation period = 8–12 years

Lepromatous & Tuberculoid Leprosy:

Clinical Features	Lepromatous Leprosy	Tuberculoid Leprosy
Skin & Nerves	Widely disseminated	One or few sites
Skin lesion:		
1. Margins	▪ Poorly defined	▪ Well-defined
2. Elevation margin	▪ Never	▪ Common
3. Color	▪ Slight hypo-pigmentation	▪ Marked hypo-pigmentation
4. Sweating & hair growth	▪ Impaired late	▪ Impaired early
Nerve enlargement & damage	Late	Early
Bacilli	Many	Absent
Natural history	Progressive	Self – limiting
Reactions	Type 2 reaction	Type 1 reaction

▪ **Leprosy Reactions:**

	<u>Lepra Reaction Type-I</u>	<u>Lepra Reaction Type-II</u>
Also Known as	Reversal reaction	Erythema nodosum leprosum
Mechanism	Cell-mediated hypersensitivity	Immune-complex mediated
Clinical Features	Painful tender nerves Loss of function Swollen skin lesions New skin lesion	Tender papules and nodules Painful tender nerves Loss of function, iritis, orchitis, myositis, lymphadenitis , fever , edema
Management	Prednisolone	Moderate = prednisolone Severe = thalidomide

▪ **Clinical Features:**

- Skin:
 - The most common skin lesions are macules or plaques.
 - **It usually manifests as hypopigmented anesthetic macules.**
 - Sensory loss is a typical feature of leprosy
 - Erythema nodosum occurs in Lepromatous Leprosy.
 - "Leonine facies" due to facial skin thickening.
- Nerve Damage:
 - Peripheral nerve trunks are damaged.
 - A thickened nerve is another feature of leprosy.
 - Damage to radial nerve results in wrist drop, common peroneal nerve results in foot drop.
 - The CNS is not affected.
- Other Features:
 - Blindness.
 - Anesthesia of cornea and conjunctiva (damage to trigeminal nerve)
 - Nasal collapse
 - Bilateral testicular atrophy causing:
 - Gynecomastia
 - Azoospermia and hypogonadism

▪ **Diagnosis:**

- The diagnosis of leprosy is essentially clinical with:
 - Hypo-pigmented patches with loss of sensation
 - Thickened peripheral nerves
 - Acid-fast bacilli on skin smears or biopsy.

R_x

Treatment:

- Multi-bacillary Leprosy (> 5 skin lesions):
 - Rifampicin 600 mg once-monthly, supervised
 - Clofazimine 300 mg once-monthly, supervised
 - Clofazimine 50 mg daily, self – administered.
 - Dapsone 100 mg daily, self – administered
 - Treatment duration is = 12 months.
- Pauci-bacillary Leprosy (2 – 5 skin lesions):
 - Rifampicin 600 mg once-monthly, supervised
 - Dapsone 100 mg daily, self – administered
 - Treatment duration is = 6 months.
- Pauci-bacillary Single Lesion (1 skin lesion):
 - Rifampicin 600 mg + Ofloxacin 400 mg + Minocycline 100 mg
 - As a single dose.

Protozoal Infections

I. Malaria:

▪ Introduction:

- It is caused by Plasmodium protozoa.
- It is transmitted by the bite of female anopheline mosquito.
- Plasmodium has four species:
 - P. falciparum = minimum incubation period is 8-25 days
 - P. vivax = minimum incubation period is 8-25 days
 - P. ovale = minimum incubation period is 8-25 days
 - P. malariae = minimum incubation period is 15-30 days.

▪ Life Cycle:

○ Pre-erythrocytic Sporogeny:

- Infective sporozoites are injected into human host by the bite mosquito.
- Sporozoites which are not destroyed by immune system are taken up by liver.
- Sporozoites multiply inside hepatocytes as merozoites.
- When infected hepatocytes rupture, merozoites are released into blood and taken up by erythrocytes.
- In the case of P. vivax and P. ovale, a few parasites remain dormant in the liver as hypnozoites, which when reactivated cause relapsing infection.

○ Erythrocytic Sporogeny:

- Inside the red cells the parasites again multiply, forming new merozoites.
- When erythrocytes rupture, merozoites are released and infect further cells.
- Each cycle of this process takes about:
 - 48 hours in P. falciparum, P. vivax, and P. ovale
 - 72 hours in P. malariae

▪ Clinical Features of Plasmodium Falciparum:

- It is the most dangerous of malarias.
- High grade fever, accompanied by rigors and drenching sweats.
- Fever has no pattern.

- Malaise, headache, vomiting,
- Jaundice, Hepato-splenomegaly
- Anemia and thrombocytopenia
- **Severe Falciparum Malaria:**
 - It is associated with high parasitemia (>2% of red cells infected).
 - It may present with:
 - Cerebral malaria (most common presentation):
 - Diminished consciousness, confusion, and convulsions,
 - Progressing to coma & death (most common cause of death in adults with malaria)
 - **Blackwater Fever:**
 - It refers to passage of dark urine (hemoglobinuria)
 - It is due to widespread intravascular hemolysis, affecting both parasitized and un-parasitized red cells.
 - Other Complications;
 - Severe anemia (< 5 g/dL)
 - DIC
 - Acute respiratory distress syndrome
 - Hypoglycemia
 - Metabolic acidosis
 - Gastrointestinal (diarrhea, jaundice, and splenic rupture)

▪ **Clinical Features of P. malariae, vivax, ovale:**

- P. malariae:
 - **Qurtan Fever** i.e. fever recurs after every 72 hours.
 - It is associated with glomerulonephritis and nephrotic syndrome.
- P. vivax & ovale:
 - It referred to as "**Benign Tertian Malaria**".
 - Fever spikes every 48 hours.
 - Anemia develops slowly with tender Hepatosplenomegaly.
 - Hypnozoites in liver can cause relapses for many years after infection.

▪ **Diagnosis:**

- Giemsa-stained thick and thin blood films.
 - Thick film shows all blood stages of parasite.
 - Thin film is essential:

- To confirm diagnosis
- To identify the species of parasite
- To quantify parasitic load in *P. falciparum* infection
- Rapid Stick Tests:
 - Immunochromatographic tests for malarial antigens such as:
 - OptiMal= detects plasmodium lactate dehydrogenase of several species
 - ParasightF = detects *P. falciparum* histidine-rich protein 2.

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Treatment:

(i). *P. vivax, ovale, malariae*:

- The drug of choice for susceptible parasites is chloroquine.
- *P. vivax, ovale*, and *malariae* are almost always susceptible to this drug.
- Treatment Regimen:
 - Chloroquine 600 mg
 - 300 mg 6 hours later, 300 mg 24 hours later, 300 mg 24 hour later.
- *P. vivax* and *ovale* are associated with relapses due to presence of hypnozoites in the liver. Therefore infection with these agents require course of "Primaquine", which destroys the hypnozoit phase in the liver.

(ii). *P. falciparum*:

- Almost all are resistant to chloroquine & sulfadoxine-pyrimethamine (Fansidar).
- Uncomplicated *P. falciparum*:
 - Drug of Choice:
 - Artemisinin-based chemotherapy – OR
 - Quinine
 - Regimen 1:
 - Co-artemether (artemether + lumefantrine)
 - 4 tables at 0, 8, 24, 36, 48, and 60 hours (3 days).
 - Regimen 2:
 - Quinine 600 mg 3 times daily for 7 days, PLUS
 - Doxycycline 200 mg x 1 daily for 7 days – OR:
 - Clindamycin 450 mg x 3 daily for 7 days – OR:

- Atovaquone-proguanil 4 tablets x once daily x 3 days.
 - **Complicated P. falciparum:**
 - IV artesunate 2.4 mg/kg at 0, 12, and 24 hours, then once daily for 7 days.
 - However, once the patient is stable enough to take orally, switch to oral artesunate 2 mg/kg once daily (complete a total cumulative dose of 17 – 18 mg/kg).
- OR:
- Quinine salt: loading dose 20 mg/kg infused over 4 hours, followed by maintenance dose of 10 mg/kg over 4 hours every 8 hours
 - The loading dose should not be given if the patient has received quinine, quinidine, or mefloquine during the previous 24 hours.

Chemoprophylaxis of Malaria

<u>Anti-Malarial Drugs</u>	<u>Dose</u>	<u>Regimen</u>
<u>High Chloroquine Resistance:</u> <ul style="list-style-type: none"> ▪ Mefloquine – OR: ▪ Doxycycline – OR: ▪ Malarone 	250 mg weekly 100 mg daily 1 tablet daily	Start 2-3 wks before & continue until 4 wks after travel. Start 1 wk before & continue until 4 wks after travel. Start 1-2 days before & continue until 1 wk after return.
<u>Low Chloroquine Resistance:</u> <ul style="list-style-type: none"> ▪ Chloroquine, AND: ▪ Proguanil 	300 mg weekly 100-200 mg daily	Start 1 week before & continue until 4 wks after travel.

II. Kala-Azar:

■ Introduction:

- Also known as "Visceral Leishmaniasis".
- It is caused by the protozoan *Leishmania donovani* complex.
- It is transmitted by phlebotomine sandfly.
- Incubation period is usually 1 – 2 months, but may be several years.

■ Clinical Features:

- Fever – initially with rigors and chills; frequency decreases over time.
- Massive splenomegaly
- Hepatomegaly
- Lymphadenopathy
- Blackish discoloration of skin
- Edema and ascites – due to Hypoalbuminemia
- Hematologic abnormalities:
 - Anemia
 - Thrombocytopenia
 - Pancytopenia

■ Diagnosis:

- CBC = pancytopenia with granulocytopenia and monocytosis
- LFTs = Hypoalbuminemia
- Immunology = hyper-gammaglobulinemia (IgG first then IgM)
- Splenic/Bone marrow/Lymph node/Liver Biopsy:
 - It is diagnostic test of choice with 98% sensitivity.
 - It shows amastigotes called "Leishman – Donovan bodies".

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Treatment:

- Drug of choice is pentavalent antimony salts – e.g. sodium stibogluconate
- Resistant cases are treated with intravenous amphotericin B (liposomal form)
- Other agents:
 - Miltefosin
 - Paromomycin
 - Pentamidine

III. Amoebiasis:

■ Introduction:

- It is caused by *Entamoeba histolytica*.
- It exists both as a motile trophozoite and as a cyst.
- Cysts are transmitted by ingestion of contaminated food, water, person-to-person.
- Trophozoites emerge from cysts in the small intestine and then pass on to the colon, where they multiply causing intestinal amoebiasis.

■ Clinical Features:

- Amebic dysentery (bloody diarrhea)
- Tenesmus, abdominal pain
- With or without liver abscess
- Systemic symptoms e.g. headache, nausea, and anorexia may be present.

■ Diagnosis:

- Fresh stool sample:
 - Motile trophozoites containing red blood cells must be identified.
 - Presence of amoebic cysts alone does not imply disease.
- Sigmoidoscopy = typical flask-shaped ulcers.
- Amoebic fluorescent antibody test is positive in at least 90% of patients with liver abscess and 60 – 70% with active colitis.

R_x

Treatment:

- Metronidazole 800 mg x 3 times daily for 5 days.
- Diloxanide Furoate:
 - It is given orally for 10 days.
 - It is a luminal amoebicide given to clear the bowel of parasites.

IV. Giardiasis:

■ Introduction:

- It is caused by *Giardia intestinalis* (aka *Giardia lamblia*).
- Mode of transmission = fecal – oral route
- Incubation period is 1 – 3 weeks.

- The parasites attach to duodenal and Jejunal mucosa, causing inflammation.

■ **Clinical Features:**

- Watery diarrhea
- Nausea, anorexia, and abdominal discomfort and bloating
- Abdominal distention and tenderness
- Malabsorption (weight loss and steatorrhea)

■ **Diagnosis& Treatment:**

- Stool sample:
 - Both cysts and trophozoites can be found.
 - Negative stool examination does not exclude diagnosis.
- Treatment:
 - Single dose of tinidazole 2g once daily for 3 days. OR
 - Single dose of metronidazole 2g once daily for 3 days.

Liver Abscess

I. Pyogenic Liver Abscess:

- It is uncommon, but important, because it is potentially curable and inevitably fatal if untreated.
- Infection reaches the liver through:
 - Hepatic circulation; Portal circulation
 - Biliary tree; Injury or direct spread from adjacent organs

▪ Causes:

- Biliary disease (most common)
 - Ascending infection due to biliary obstruction (cholangitis)
 - Contagious spread from an empyema of gallbladder
- Colonic Disease:
 - Diverticulitis
 - Crohn's disease
- Other Causes:
 - Pancreatitis; Intra-abdominal sepsis
 - Traumatic introduction

▪ Bacteriology:

- Most common agents = E. coli & streptococcus milleri
- Streptococcus fecalis
- Bacterioids
- Klebsiella pneumoniae

▪ Clinical Features:

- High grade fever, with rigors and chills
- Right upper quadrant pain, radiating to right shoulder - most common symptom
- Tender hepatomegaly
- Jaundice

▪ Diagnosis:

- US abdomen – visualizes > 90% of abscesses (multiple abscesses)
- Leukocytosis
- Plasma alkaline phosphatase is raised

- Hypoalbuminemia
- Chest X-ray:
 - Raised right diaphragm and lung collapse
 - Or effusion at the base of the right lung.

Rx

Treatment:

- Combination of antibiotics e.g. ampicillin + gentamicin + metronidazole
- US-guided drainage of abscess if:
 - No response to medical therapy
 - Abscess is large

II. Amoebic Liver Abscess:

- It is the most common extra-intestinal manifestation of amoebiasis.
- It occurs when trophozoite enters portal venous circulation by burrowing through the large bowel mucosa.
- **Clinical Features:**
 - Right upper quadrant abdominal pain.
 - Pain radiating to right shoulder.
 - Tender hepatomegaly.
 - In contrast to pyogenic liver abscess there is:
 - Absence of toxicity
 - High swinging fever
 - Single abscess (most commonly affecting the right lobe)
 - Complications:
 - Rupture in to the lungs and pleural cavity.
 - Rupture in to peritoneal cavity or pericardial cavity is less common
- **Diagnosis:**
 - CBC = neutrophil leukocytosis
 - US abdomen = visualizes liver abscess
 - Detectable antibodies in 95% of patients.

Rx

Treatment:

- Metronidazole + Diloxanide furoate
- Surgical drainage is required when:
 - Failure to respond to medical therapy
 - Presence of complications

III. Hydatid Liver Disease:

- It is caused by larval forms of cestode (tapeworm), Echinococcus granulosus.
- It can affect any organ, but liver is the most common, followed by the lung.
- **Clinical Features:**
 - It is typically acquired in childhood.
 - It causes cysts in the liver (75%), lung, bone, or brain.
 - It may be asymptomatic.
 - It presents with painful mass in the liver.
 - It can present acutely in the form of anaphylactic shock due to rupture of the cyst.
- **Diagnosis:**
 - CBC = eosinophilia
 - Serology:
 - Casoni test is positive in 80% of cases.
 - Indirect hemagglutination is the most accurate test.
 - CT scan:
 - It is the imaging modality of choice.
 - It shows space-occupying lesion with a smooth outline with septa.

Rx

Treatment:

- Medical treatment = albendazole 400 mg x 3 times daily for 30 days.
- Surgical Treatment:
 - If ERCP shows connection between cyst and bile duct = removal of intact cyst.
 - If ERCP shows no connection between cyst and bile duct = PAIR i.e.:
 - Puncture of cyst
 - Aspiration of cyst
 - Injection of 100% ethanol or hypertonic saline
 - Re-aspiration after 25 minutes.

Sexually Transmitted Diseases (STDs)

I. Syphilis:

- It is an STD caused by a spirochete *Treponema pallidum*.
- **Clinical Features:**
 - **Primary Syphilis:**
 - It occurs 9 – 90 days after infection.
 - It presents with Chancre i.e. painless ulcer, with clean base, raised, indurated borders, usually in the genital area.
 - Draining lymph nodes may be enlarged, mobile and rubbery.
 - Both chancre and lymph nodes are PAINLESS.
 - Without treatment, the chancre will resolve within 2- 6 weeks.
 - **Secondary Syphilis:**
 - It occurs 6 – 8 weeks after chancre.
 - It presents with low-grade fever, headache, malaise, and generalized non-tender lymphadenopathy.
 - **"Snail track ulcer" in the mouth.**
 - Non-pruritic, symmetrical maculopapular rash on the soles and palms.
 - Without treatment the rash may last for up to 12 weeks.
 - **Condylomata Lata:**
 - Flat wart-like peri-anal and mucous membrane lesions.
 - Highly contagious
 - **Latent Syphilis:**
 - It refers to positive syphilis serology with no evidence of clinical disease.
 - It is divided into two phases:
 - Early Latent Syphilis:
 - No symptoms, positive serology within 2 years of infection
 - Patient is sexually infectious.
 - Late Latent Syphilis:
 - No symptoms, after 2 years of infection.
 - Patient is NOT sexually infectious.

○ **Tertiary Syphilis:**

- It occurs between 3 – 10 years after infection.
- The characteristic feature is a chronic granulomatous lesion called a "gumma".
- The classic features are:
 - General paresis (dementia)
 - Cardiovascular findings (aortic root aneurysm, aortic regurgitation)
 - Neurosyphilis (Tabes Dorsalis, Argyll-Robertson pupil, Meningo-vascular stroke)

▪ **Diagnosis:**

- Dark-field microscopy = identifies motile spirochetes in primary & secondary syphilis.
- Non-specific Tests:
 - VDRL test (venereal diseases research laboratory)
 - RPR test (rapid plasma reagin)
- Specific Test:
 - FTA-ABS test (fluorescent treponemal antibody-absorbed test)
 - TP-EIA test (treponemal antigen-based enzyme immunoassay test)

R_x

Treatment:

- Penicillin is the drug of choice for all the stages of syphilis.
- Doxycycline is used for penicillin-allergic patients.
- Pregnancy:
 - Penicillin is the drug of choice.
 - Penicillin-allergic patients:
 - Penicillin de-sensitization, followed by penicillin, OR
 - Erythromycin for pregnant woman and penicillin for newborn baby (to protect baby from syphilis as erythromycin crosses placenta poorly)

II. Gonorrhea:

- It is caused by *Neisseria gonorrhoeae*:
 - It is a gram-negative diplococcus.
 - Incubation period is 2 – 10 days.
 - Mode of transmission = vaginal, anal, or oral sex

▪ **Clinical Features:**

- In men:
 - It commonly involves the anterior urethra.
 - Urethritis with purulent urethral discharge.
 - Dysuria; proctitis
- In women:
 - 80% of women who have gonorrhea are asymptomatic.
 - Greenish-yellow discharge.
 - Adnexal or pelvic pain.
 - Disease spectrum is as follows:
 - Vulva = Skene gland adenitis.
 - Vagina = Vaginitis
 - Cervix = Acute cervicitis
 - Uterus = Acute endometritis
 - Fallopian tube = Acute salpingitis

▪ **Complications:**

- Acute prostatitis and epididymo-orchitis in men
- Bartholin's gland abscess
- Ectopic pregnancy
- Disseminated Gonococemia:
 - Monoarticular septic arthritis
 - Rash – hemorrhagic, painful pustules.
 - Tenosynovitis

▪ **Diagnosis & Treatment:**

- Gram stain and culture is the Gold Standard.
- NAAT of urine.
- Treatment:
 - Cefixime, OR
 - Ceftriaxone (contraindicated during pregnancy)

III. Chlamydia:

- It is caused by Chlamydia trachomatis; an obligate intracellular bacterium.
- **Serotypes:**
 - Serotypes A,B,C = Trachoma (follicular conjunctivitis with corneal scarring)
 - Serotypes L1-L3 = Lymphogranuloma venereum

- Serotypes D – K:
 - Causes STD.
 - Characterized by urethritis, cervicitis, or pelvic inflammatory disease (PID).
- **Clinical Features:**
 - 80% of women who have chlamydia are asymptomatic.
 - Mucopurulent cervical discharge (classic finding)
 - Cervical motion tenderness.
 - Intermenstrual or post-coital bleeding
 - Complications:
 - Reiter's syndrome = urethritis, conjunctivitis, arthritis
 - Fitz-Hugh-Curtis Syndrome = peri-hepatic inflammation and fibrosis.
 - Infertility & ectopic pregnancy = from PID.
- **Diagnosis:**
 - Diagnosis is usually clinical.
 - Gram stain of discharge may show neutrophils, but no bacteria (intracellular)
 - **Culture is the Gold Standard.**
 - Nucleic acid amplification test (NAAT) of urine for rapid diagnosis.
- **Treatment:**
 - Azithromycin 1gm orally as a single dose, OR
 - Doxycycline orally for 7 days.

IV. Human Papilloma Virus (HPV):

- HPV has over 90 genotypes.
- HPV-6, 11, 16, and 18 most commonly infect the genital tract through sexual transmission.
- **Clinical Features:**
 - Genotypes 6 and 11:
 - Cause ano-genital warts, which may be single, multiple, exophytic or flat.
 - **Buschke – Lewenstein tumor** refers to a giant condyloma with local tissue destruction.

- Genotypes 16 and 18:
 - Cause dysplastic conditions and cancers of genital tract
 - Can affect penis, vulva, vagina, cervix, perineum, or anus.

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Treatment:

- Podophyllotoxin = for home treatment of external warts (contraindicated in pregnancy)
- Imiquimod cream = for home treatment of external warts (contraindicated in pregnancy)
- Cryotherapy = for treatment of internal and external warts
- Hyfrecation (electrofulgration that causes charring) = for external & internal warts
- Surgical removal
- Prevention:
 - Bivalent vaccine = protection against HPV-16, 18
 - Quadrivalent vaccine = protection against HPV-6, 11
 - Current recommendation are:
 - HPV should be administered prior to the onset of sexual activity.
 - Typically at age 11 – 13, in a course of 3 injections.

V. Sexually Transmitted Genital Lesions:

▪ Granuloma Inguinale:

- Also known as “Donovanosis”.
- It is caused by *Klebsiella granulomatis*.
- Clinical Features:
 - Beefy-red ulcer; hypertrophic granulomatous lesions
 - Painless
- Diagnosis = Biopsy (Donovan bodies), which are intracellular bipolar staining bodies.
- Treatment:
 - Azithromycin, OR
 - Doxycycline

▪ Chancroid:

- It is caused by *Hemophilus ducreyi*; a gram-negative rod.

- Clinical Features:
 - Painful ulcers (mnemonic: you cry with ducreyi).
 - Ulcers are irregular, deep, and well-demarcated with **ragged undermined edge**.
 - Inguinal lymph nodes are tender, unilateral, matted and unilocular.
- Treatment:
 - Single dose of oral azithromycin. OR
 - Single dose of IM ceftriaxone.

▪ **Lymphogranuloma Venereum (LGV):**

- It is caused by chlamydia trachomatis serotypes L1, 2, 3.
- Clinical Features:
 - Painless ulcer.
 - Ulcer is small, transient and often unnoticed.
 - Inguinal lymph nodes are tender, unilateral, matted, but multilocular.
- Treatment:
 - Doxycycline, OR
 - Erythromycin

HIV, AIDS & Complications

HIV Infection & AIDS:

I. Introduction:

▪ Virology:

- HIV stands for human immunodeficiency virus.
- AIDS stands for acquired immunodeficiency syndrome.
- AIDS is caused by:
 - HIV-1:
 - HIV is a single-stranded RNA retrovirus.
 - HIV belongs to Lentivirus group of retrovirus family.
 - HIV-2:
 - It causes less aggressive disease than HIV-1.
 - It is restricted mainly to western Africa.

▪ Pathogenesis:

- The virus attaches to the surface of **CD4 (Helper) T-cells**.
- The virus then enters the cell and uncoats, and its RNA is transcribed to DNA by reverse transcriptase.
- The virus destroys CD4 T-cells and therefore weakens cell – mediated immunity.
- Each day:
 - $> 10^{10}$ virions are produced i.e. daily turnover of 30% of total viral burden.
 - $> 10^9$ CD4 T-cells are destroyed i.e. 6-7% of total body CD4 cells.

▪ Mode of Transmission:

- Sexual:
 - Man-to-man
 - Heterosexual (most common route accounting for $> 75\%$)
 - Oral
- Parenteral:
 - Blood (transmission risk is 90%)
 - Injection drug users
 - Occupation injury

- Vertical:
 - Vertical transmission occurs during pregnancy, during birth, and breastfeeding
 - Vertical transmission is higher in developing countries (25-44%) than in industrialized countries (13-25%).
 - 80% of vertical transmission occurs during child birth (labour)
 - 20% of vertical transmission occurs in utero.

II. Classification of HIV:

- HIV can be broadly classified into following types depending on clinical features:
 - Primary infection
 - Asymptomatic infection
 - Mildly symptomatic infection
 - Acquired immunodeficiency syndrome (AIDS)
- **Primary Infection:**
 - Primary infection is symptomatic in 70-80% of cases.
 - Primary infection usually occurs 2 – 6 weeks after exposure.
 - Primary infection coincides with:
 - High plasma HIV-RNA levels
 - Fall in CD4 count to 300 – 400 cells/mm³
 - Clinical Features:
 - Fever with rash
 - Pharyngitis with cervical lymphadenopathy
 - Myalgias and arthralgias
 - Headache and mucosal ulceration
- **Asymptomatic Infection:**
 - It is category-A disease in Centers for Disease Control (CDC) Classification.
 - The patient is seropositive, but no evidence of disease.
 - The patient may have persistent generalized lymphadenopathy (PGL).
 - **PGL is defined as enlarged glands at ≥ 2 extra-inguinal sites.**
 - CD4 counts are normal ($> 500/\text{mm}^3$)
 - CD4 count declines at a rate of 50 – 150 cells per year.
- **Mildly Symptomatic Disease:**
 - It is category-B disease in Centers for Disease Control (CDC) Classification.

- It presents with symptoms and diseases that are NOT AIDS-defining illness, such as:
 - Oral hairy leukoplakia
 - Recurrent Oropharyngeal candidiasis
 - Recurrent vaginal candidiasis
 - Bacillary angiomatosis
 - Idiopathic thrombocytopenic purpura
 - Weight loss
 - Herpes zoster
 - Chronic diarrhea

▪ **AIDS:**

- It is category-C disease in Centers for Disease Control (CDC) Classification
- **AIDS is defined by HIV with CD4 count $< 200/\text{mm}^3$ or opportunistic infections or malignancy.**
- AIDS-defining diseases are:
 - Esophageal candidiasis (not Oropharyngeal)
 - Cryptococcal meningitis
 - Cryptosporidial diarrhea
 - Cerebral toxoplasmosis
 - Cytomegalovirus retinitis
 - Disseminated mycobacterium avium intracellulare (MAI)
 - Pulmonary or extra-pulmonary TB
 - Pneumocystis carinii (jirovecii) pneumonia (PCP)
 - Extra-pulmonary coccidioidomycosis
 - Extra-pulmonary Histoplasmosis
 - Progressive multifocal leukoencephalopathy (PML)
 - Malignancy:
 - Non-Hodgkin lymphoma
 - Kaposi's sarcoma (most common)
 - Primary cerebral lymphoma.
 - Invasive cervical cancer

III. Investigations:

▪ **Diagnosis:**

- **Best initial test = ELISA test.**
- **Confirmatory test = Western blot**
- Infected Infants:
 - Diagnosed by PCR-RNA or viral culture

- ELISA testing is unreliable because maternal HIV antibodies may be present for up to 6 months after delivery.

▪ Viral Load:

- PCR-RNA viral load test is used to:
 - Measure response to therapy (decreasing levels are good)
 - Detect treatment failure (increasing levels are bad)
 - Diagnose HIV in infants

IV.

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Treatment:

▪ Indications for Treatment:

- CD4 count and Indications for Treatment:
 - ≥ 350 cells/mm³:
 - Monitor 3 – 6 monthly
 - Consider treatment if hepatitis B or C co-infected or > 55 years of age
 - < 350 cell/mm³:
 - $350 - 200$ cells/mm³ = treat as soon as patient is ready
 - < 200 cells/mm³ = treat as soon as possible
- Primary Infection and Indicator for Treatment:
 - Start treatment if:
 - There is neurologic involvement
 - CD4 count is < 200 cells/mm³ for > 3 months
 - AIDS-defining disease

▪ Choice of Drugs:

- Treatment of HIV is referred to as highly active retroviral therapy (HAART).
- HAAR involves use of ≥ 3 drugs for better outcome and to decrease resistance.

Regimen 1:

- Two nucleoside reverse transcriptase inhibitors (NRTI), PLUS
- Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Example:
 - Efavirenz + Tenofovir + Emtricitabine

Regimen 2:

- Two nucleoside reverse transcriptase inhibitors (NRTI), PLUS
- Boosted protease inhibitor (PI).
- Example:
 - Ritonavir – boosted Atazanavir + Tenofovir + Emtricitabine

Regimen 3:

- Two nucleoside reverse transcriptase inhibitors (NRTI), PLUS
- Integrase Inhibitor (II), which inhibits final step of pro-viral DNA integration
- Example:
 - Raltegravir (II) + Tenofovir + Emtricitabine

Anti-Retroviral Drugs	
Drugs	Side-effects
<u>Nucleotide Reverse Transcriptase Inhibitors (NRTI):</u>	
Tenofovir Abacavir Didanosine Zidovudine Lamivudine Emtricitabine Stavudine	NRTI (whole class): <ul style="list-style-type: none"> • Gastrointestinal intolerance • Lipoatrophy • Lactic acidosis Zidovudine = bone marrow suppression Stavudine & Didanosine = peripheral neuropathy and pancreatitis Tenofovir = renal insufficiency Abacavir = hypersensitivity, check for HLA-B*5701.
<u>Non-nucleotide Reverse Transcriptase Inhibitors (NNRTI):</u>	
Efavirenz Etravirine Nevirapine	NNRTI (whole class): <ul style="list-style-type: none"> Rash Hepatitis Efavirenz: <ul style="list-style-type: none"> CNS effects (hallucinations, depression) Contraindicated in pregnancy
<u>Protease Inhibitors:</u>	
Atazanavir Indinavir Ritonavir Saquinavir	PI (whole class): <ul style="list-style-type: none"> Gastrointestinal intolerance, hepatotoxicity Type-II diabetes, truncal obesity Indinavir = crystalluria and nephrolithiasis

■ **Treatment During Pregnancy:**

- All pregnant women should routinely be recommended for HIV testing.
- The medications used are same as that for non-pregnant EXCEPT for Efavirenz, which is contraindicated due its teratogenicity.
- Therefore instead of Efavirenz a protease inhibitor should be used.
 - If mother is HIV positive and is already taking HAART then continue medications.
 - If mother is HIV positive with CD4 < 350 and HIGH viral load and is not on HAART:
 - Start treatment immediately
 - Zidovudine + Lamivudine + Protease inhibitor
 - If mother is HIV positive with CD4 ≥ 350 and LOW viral load and is not on HAART:
 - Treatment is still required to reduce vertical transmission.
 - Anti-retrovirals between 2nd & 3rd trimester and stopping after birth.
 - Zidovudine monotherapy (starting from 12-14 weeks) if viral load is low (<10,000 copies/mL) and Caesarean section is planned.
- Other Measures to Reduce Vertical Transmission:
 - Caesarean section if CD4 is low, viral load is high, and patient not on HAART
 - Caesarean section is not required if patient is on HAART and viral load is low.
 - **Avoid breastfeeding**
 - Transmission rates:
 - < 1% = for Zidovudine monotherapy + Caesarean section
 - < 1% = for HAART and planned vaginal delivery when viral load is < 50 copies/mL.

■ **Post-exposure Prophylaxis:**

- It is required for healthcare workers following occupational exposure to HIV.
- It is also required for non-occupation exposure (e.g. victims of rape, sexual exposure)
- British Recommendations:
 - **Agents = Zidovudine + Lamivudine + Lopinavir/Ritonavir.**
 - **Duration = 4 weeks**

HIV-Related Opportunistic Infections:

I. Pneumocystis Jirovecii Pneumonia (PCP):

- It is a fungal pneumonia, accounting for 25% of AIDS-defining illness.
- It occurs in patients with AIDS whose CD4 count is < 200 cell/mm³.
- **Clinical Features:**
 - Progressive exertional dyspnea
 - Fever, dry cough, and difficulty in taking deep breath.
- **Diagnosis:**
 - CXR = bilateral interstitial infiltrates
 - ABGs = increased alveolar-arterial (A-a) gradient
 - Increased lactate dehydrogenase (LDH)
 - Most accurate test = Bronchoalveolar lavage (BAL)

R_x

Management:

- Prophylaxis:
 - **Start prophylaxis when CD4 count is < 200 cells.**
 - Agent is Trimethoprim-Sulfamethoxazole (TMP-SMX) i.e. co-trimoxazole
 - Stop prophylaxis when CD4 count is > 200 /mm³ for ≥ 3 months.
- Treatment of infection:
 - **Drug of choice is TMP-SMX**
 - Severe Infection refers to PO₂ < 70 mmHg or A-a gradient > 35 .
 - Severe infection is treated by:
 - Steroids + TMP-SMX, OR
 - Steroids + Clindamycin + Primaquine
 - Stop treatment when CD4 count is > 200 /mm³ for ≥ 3 months.

II. Pulmonary Tuberculosis:

- TB is the most common global infection, affecting up to one-third of HIV patients.
- Both pulmonary and extra-pulmonary TB are considered AIDS-defining illness.
- At – risk CD4 count = any, with risk increasing as count falls.
- Clinical features of TB are already discussed in chapter of respiratory diseases.

Rx

Management:

- Prophylaxis:
 - Start prophylaxis when PPD is > 5 mm, or “high-risk” exposure
 - Agent is Isoniazid (+pyridoxine) for 9 months.
- Treatment of active disease:
 - Start anti-tuberculous therapy (ATT) with isoniazid, rifampicin, ethambutol & pyrazinamide for 2 months, then rifampicin and isoniazid for 4 months.

III. Disseminated Mycobacterium avium intracellulare (MAI):

- It occurs when CD4 count is < 50 cells/mm³.
- **Clinical Features:**
 - Fever, night sweats, weakness, and weight loss.
 - Hepatosplenomegaly and lymphadenopathy
 - Diarrhea and pancytopenia.
 - Diagnosis:
 - Obtain mycobacterial blood cultures.
 - Anemia, Hypoalbuminemia, and **increased serum alkaline phosphatase.**
 - Biopsy of bone marrow, intestine, or liver shows foamy macrophages with acid-fast bacilli

Rx

Management:

- Prophylaxis:
 - Start prophylaxis when CD4 < 50 /mm³.
 - Agent is azithromycin weekly.
 - Stop prophylaxis when CD4 > 100 /mm³ for > 6 months.
- Treatment of active disease:
 - Clarithromycin + Ethambutol ± Rifabutin.
 - Stop after 12 months and until CD4 is > 100 /mm³ for > 6 months.

IV. Toxoplasmosis:

- It is caused by *Toxoplasma gondii*.
- It occurs after ingesting raw or undercooked meat and changing cat litter.
- **Clinical Features:**
 - Cerebral toxoplasmosis is an AIDS-defining illness.
 - **Cerebral toxoplasmosis occurs when CD4 is $< 100/\text{mm}^3$**
 - It may present with altered mental status, focal neurologic signs, fever, headache, or seizures.
 - Diagnosis:
 - Positive toxoplasma serology
 - Brain CT (MRI) shows;
 - **Multiple ring-enhancing mass lesions**
 - **Lesions have predilection for basal ganglia**



Management:

- Prophylaxis:
 - Start prophylaxis when CD4 is $< 100/\text{mm}^3$ + positive toxoplasma IgG serology
 - Agent is trimethoprim-sulfamethoxazole (TMP-SMX)
- Treatment of active disease:
 - **Pyrimethamine + Sulfadiazine + Leucovorin for 6 weeks.**
 - Leucovorin is a folic acid analogue given to prevent hematologic toxicity.
 - Stop therapy when CD4 $> 200/\text{mm}^3$ for 3 months on suppressive HAAR.

V. Progressive Multifocal Leukoencephalopathy (PML):

- It is an AIDS-defining illness.
- It occurs when CD4 is $< 50 /\text{mm}^3$.
- **Clinical Features:**
 - It may present with altered mental status, focal neurologic signs, fever, headache, or seizures
 - Diagnosis:
 - CSF = JC polyomavirus PCR-positive
 - Brain CT (MRI) shows;
 - **Multiple, bilateral, asymmetric NON-enhancing mass lesions**

R_X

- Lesions have predilection for white matter; no edema or mass effect

Management:

- Prophylaxis = none
- Treatment = HAART

VI. Primary CNS Lymphoma:

- It is an AIDS defining illness.
- It is a high-grade, diffuse, B-cell lymphoma.
- It occurs when CD4 is $< 50 /\text{mm}^3$.
- **Clinical Features:**
 - It may present with altered mental status, focal neurologic signs, headache, or seizures
 - **Fever is ABSENT.**
 - Diagnosis:
 - CSF PCR is positive for Epstein - Barr virus (EBV).
 - Biopsy is definitive diagnosis.
 - Brain CT (MRI) shows;
 - **Single, large, homogenous enhancing periventricular lesion**
 - **Edema and mass effect.**

R_X

Management:

- Treatment is with HAART and high-dose methotrexate; prognosis is very poor.
- Failure to improve clinically or on scanning with a trial of anti-toxoplasma therapy for 2- 4 weeks is consistent with primary CNS lymphoma.

VII. Cryptococcal Meningitis:

- It is caused by Cryptococcus neoformans.
- It occurs when CD4 is $< 200 /\text{mm}^3$.
- **Clinical Features:**
 - Headache, fever, impaired mental status, drowsiness, confusion and blurred vision.
 - **Signs of meningeal irritation are ABSENT.**

- Diagnosis:
 - Lumber Puncture:
 - Cells = lymphocytes
 - Protein = raised
 - Glucose = low
 - CSF India ink stain positive for Cryptococcus in 60% cases.
 - **Positive Cryptococcal antigen testing in CSF (> 95%).**

R_x

Treatment:

- IV amphotericin B + Flucytosine for 2 weeks.
- Then fluconazole for 8 weeks.
- Stop therapy when CD4 is > 200 cells/mm³, for 3 months on suppressive HAART and negative cultures.

VIII. Kaposi's Sarcoma:

- It is AIDS-defining illness, caused by **human herpes virus-8 (HHV-8)**.
- It can occur at any CD4 count level.
- **Clinical Features:**
 - Cutaneous:
 - Purple, non-pruritic papules, especially on nose, legs, and genitals.
 - Crease-line distribution over the trunk; lymphadenopathy and edema.
 - Oral & GI Tract:
 - Purple raised lesions on palate, gums, esophagus, stomach, and large bowel.
 - Hepatosplenomegaly
 - Pulmonary:
 - Breathlessness, cough, and hemoptysis; chest pain and fever
 - CXR = disease affects middle and lower zones.

R_x

Treatment:

- Cutaneous and oral disease = HAART, radiotherapy for localized disease.
- Cyclical liposomal doxorubicin for:
 - Visceral and widespread disease
 - HAART-unresponsive oral and cutaneous disease

CD4 Count & Opportunistic Infections

<u>AIDS-defining Illness</u>	<u>CD4 Count (cell/mm³)</u>
Pneumocystis carinii pneumonia (PCP)	< 200
Tuberculosis	Any, increases with decreased count
Disseminated mycobacterium avium intracellulare	< 50
Cerebral toxoplasmosis	< 100
Primary multifocal leukoencephalopathy	< 50
Primary CNS lymphoma	< 50
Cryptococcal meningitis	< 200
Cytomegalovirus retinitis	< 50

Clinical Pearl:

HIV & AIDS:

- All HIV infections do not cause AIDS.
- AIDS refers to HIV + (CD4 count < 200/mm³, OR, opportunistic infections, OR, malignancy).
- Vaccination in patients with HIV infection:
 1. Streptococcus pneumoniae:
 - Vaccination indicated in all patients.
 - Give every 5 years provided that CD4 is > 200/mm³
 2. Influenza
 - Vaccination indicated in all patients.
 - Give annually

Chapter 3

BIOCHEMISTRY



Electrolyte Disorders

Introduction:

▪ Total Body Water (TBW):

- It is 60% of the body weight in kg i.e. $TBW = \text{bodyweight} \times 60\%$
- It has following distribution:
 - Intracellular Fluid (ICF) = 40% of body weight in kg
 - Extracellular Fluid (ECF) = 20% of body weight in kg
- ECF is subdivided into:
 - Interstitial compartment
 - Intravascular compartment (plasma)
- Na is the major ECF cation; Cl is the major, while bicarbonate is the minor anion
- K is the major ICF cation; PO_4^{2-} is the major anion

▪ Plasma Osmolality (POsm):

- It is the number of solutes in plasma (i.e. tonicity of ECF)
- $POsm = 2 (Na) + \text{serum glucose}/18 + \text{serum BUN}/2.8$
- $POsm = 275 - 295 \text{ mOsm/kg}$.
- Isotonic state = normal POsm
- Hypotonic state = decreased POsm
- Hypertonic state = increased POsm

Disorders of Sodium Balance:

I. Hypernatremia:

- It refers to serum sodium of $> 145 \text{ mEq/L}$.
- It reflects an inadequacy of kidney in concentrating the urine in the face of relatively restricted water intake.
- **Clinical Features:**
 - Thirst
 - Neurologic symptoms:
 - Mental status changes
 - Weakness
 - Focal neurologic deficits
 - Seizures
- **Causes:**
 - Hypovolemic Hypernatremia (i.e. Na deficit with relatively greater water deficit)
 - Renal Na loss (e.g. diuretics)
 - GI Na loss (e.g. colonic diarrhea)
 - Skin Na loss (e.g. excessive sweating)
 - Glycosuria (HONK)
 - Euvolemic Hypernatremia:
 - It refers to water-deficit alone.
 - It is caused by diabetes insipidus (central or nephrogenic)
 - Hypervolemic Hypernatremia (i.e. Na retention with relatively less water retention):
 - Chronic renal failure (during water restriction)
 - Enteral or parenteral nutrition
 - Oral or IV salt administration

R_x

Treatment:

- Treat underlying cause.
- Replace free-water deficit depending on volume status.
- Free-water deficit = $([Na]/140 - 1) \times TBW$
 - Hypovolemia:
 - Vitally stable = use 5% dextrose water
 - Vitally unstable = use isotonic NaCl (0.9% NaCl) before correcting free-water deficit
 - Euvolemia:
 - Isotonic 5% dextrose water, OR
 - Hypotonic 0.45% NaCl.
 - Hypervolemia:
 - Diuretic, PLUS
 - 5% dextrose water

Clinical Pearl:

Chronic Hypernatremia:

- Correction of chronic hypernatremia (> 36-48 hours) should be accomplished gradually over 48-72 hours (≤ 5 mEq/L/hr) to prevent neurologic damage secondary to cerebral edema.

II. Hyponatremia:

- It refers to serum sodium of < 135 mEq/L.
- Clinical Features:
 - May be asymptomatic
 - Confusion, lethargy
 - Muscle cramps, hyporeflexia
 - Can progress to seizures, coma, or brainstem herniation
- Causes:
 - Hypovolemic Hypernatremia (i.e. Na deficit with relatively smaller water deficit)
 - Urinary Na > 20 mmol/L (Na & water are lost via kidneys)
 - Addison's disease
 - Diuretic phase of renal failure
 - Diuretics (e.g. thiazides)
 - Osmolar diuretics

- Urinary Na < 20 mmol/L (Na & water are lost other than via kidneys)
 - Diarrhea
 - Vomiting
 - Fistulas
 - Burns
 - Small bowel obstruction
- Euvolemic Hyponatremia (i.e. water retention alone):
 - SIADH
 - Psychogenic polydipsia
 - Hypothyroidism
 - Alcoholism
- Hypervolemic Hyponatremia (i.e. Na retention with relatively greater water retention):
 - Congestive cardiac failure
 - Cirrhosis
 - Nephrotic syndrome
 - Renal failure

R_x

Treatment:

- Treat according to volume status.
- Hypovolemia = normal saline
- Euvolemia = water restriction
- Hypervolemia:
 - Water restriction
 - Consider diuretics
 - Cortisol replacement with adrenal insufficiency
 - Thyroid replacement with hypothyroidism
- Hypertonic Saline is indicated in the management of hyponatremia when:
 - Serum Na is < 120 mEq/L (i.e. severe hyponatremia)
 - Patient has seizures
- Chronic hyponatremia (> 72 hour duration) should be corrected slowly at ≤ 10 mmol/l/day in order to prevent "**Central Pontine Myelinolysis**", which can manifest as:
 - Paraparesis
 - Quadriparesis
 - Dysarthria
 - Coma



Clinical Pearl:

Syndrome of Inappropriate Anti-diuretic Hormone Secretion (SIADH):

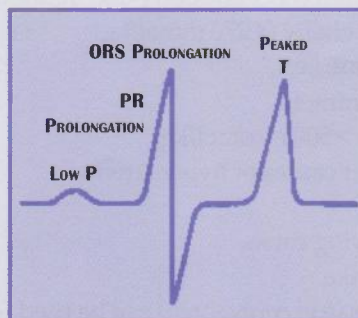
- It is an important cause of hyponatremia.
- Causes:
 - Malignancy = lung, prostate, pancreas, thymus, lymphoma
 - CNS disorders = Meningo-encephalitis, stroke, trauma
 - Chest diseases = TB, pneumonia, aspergillosis
 - Drugs: anticonvulsants (e.g. carbamazepine), antidepressants (e.g. amitriptyline), psychotropics (e.g. haloperidol), cytotoxics (e.g. cyclophosphamide)
- Diagnosis:
 - Low plasma sodium concentration (<130 mmol/L)
 - Low plasma osmolality (<270 mmol/kg)
 - Concentrated urine i.e.:
 - Urinary Na >20 mmol/L
 - Urine osmolality >500 mosmol/kg
 - Exclusion of other causes of hyponatremia
- Treatment:
 - Treat the underlying cause.
 - Restrict fluid intake.
 - ADH antagonists (e.g. conivaptan) can be used for severe, symptomatic SIADH.
 - Demeclocycline can be used for chronic SIADH.

Disorders of Potassium Balance:

I. Hyperkalemia:

- It refers to serum potassium >5 mmol/L.
- Clinical Features:
 - Nausea, vomiting, and intestinal colic
 - Muscular weakness,
 - Flaccid paralysis
 - Cardiac conduction abnormalities
 - Cardiac arrhythmias
 - ECG Findings:
 - Tall, peaked T – waves
 - Wide QRS complex
 - PR – prolongation
 - Loss of P – waves
 - Can progress to sinus waves, VF, and cardiac arrest
- Causes:
 - Decreased Excretion:
 - Renal insufficiency
 - Drugs (e.g. ACEI, Spironolactone, NSAIDs)
 - Hypoaldosteronism
 - Type – IV renal tubular acidosis (RTA)

- Re-distribution Out of Cells:
 - Tissue injury (Rhabdomyolysis)
 - Insulin Deficiency
 - Acidosis
 - Drugs (e.g. Digitalis, Beta-blockers)
 - Resorption of blood (e.g. hematomas, GI-bleeding)
- Spurious:
 - Hemolysis of blood samples
 - Fist clenching during blood draws
 - Thrombocytosis
 - Leukocytosis



Hyperkalemia

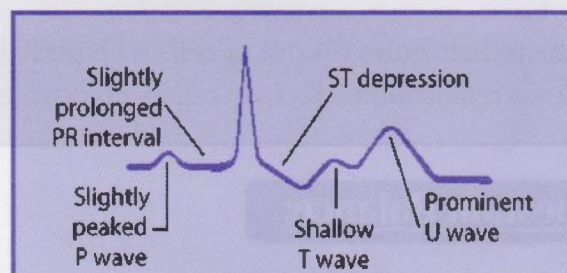
R_x

Treatment:

- Depends on severity & rate of development
- Urgent treatment is required if:
 - Acute onset
 - Severe hyperkalemia ($> 6.5 - 7 \text{ mmol/L}$)
- Step 1: Stabilize cell membrane potential:
 - IV calcium gluconate
 - 10 ml of 10% solution IV over 2 minutes.
- Step 2: Shift K into Cells:
 - IV glucose and insulin
 - Inhaled beta-2 agonist (e.g. salbutamol)
 - IV sodium bicarbonate (if acidosis present)
- Step 3: Remove K from Body:
 - IV furosemide and normal saline (if adequate renal function)
 - Ion-exchange resin (sodium polystyrene sulfonate) orally or rectally
 - Dialysis (in renal failure or severe refractory cases)

II. Hypokalemia:

- It refers to serum potassium < 3.5 mmol/L.
- **Clinical Features:**
 - Fatigue
 - Muscular weakness/cramps
 - Ascending paralysis; respiratory muscle weakness
 - Abdominal distention due to paralytic ileus
 - Hypotension; Hypo-reflexia
 - Paraesthesias
 - Cardiac arrhythmias (e.g. atrial, ventricular ectopic beats)
 - ECG Findings:
 - **Flattened T - waves**
 - U-wave
 - ST-depression

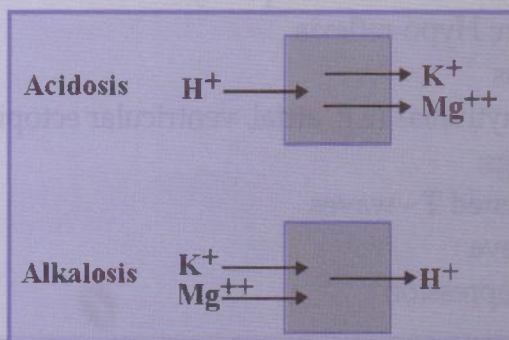


- **Causes:**
 - Re-distribution Into Cells:
 - Alkalosis
 - Insulin excess
 - Beta-2 – agonists
 - Gastrointestinal Losses (Urinary K < 20 mmol/day):
 - With alkalosis:
 - Vomiting
 - NG aspiration
 - With acidosis:
 - Diarrhea,
 - Laxative abuse
 - Villous adenoma of rectum
 - Bowel obstruction/fistula
 - Renal Losses (Urinary K > 20 mmol/day)
 - Diuretics (loop or thiazides), DKA
 - Hyperaldosteronism
 - Decreased circulatory volume
 - Hypomagnesaemia

Rx

Treatment:

- Treat the underlying disorder.
- Oral and/or IV potassium replacement
- Magnesium replacement, if hypomagnesemia present.



Acidosis redistributes K^+ out of cells = Hyperkalemia

Alkalosis redistributes K^+ into cells = Hypokalemia

Disorders of Magnesium Balance:

I. Hypomagnesemia:

■ Clinical Features:

- Similar to hypocalcemia
- Tetany
- Arrhythmias especially torsades de pointes
- Seizures
- Hypomagnesemia is associated with hypocalcemia, hyponatremia, and hypokalemia

■ Causes:

- Starvation
- Parenteral nutrition
- GI loss (vomiting, diarrhea, fistula)
- Renal loss (diuretics, alcohol, acute tubular necrosis)
- Acute pancreatitis

Disorders of Acid – Base Balance

R_x**Treatment:**

- Treat the underlying cause.
- Oral magnesium is poorly absorbed and may cause diarrhea
- If disease is symptomatic, treat with IV magnesium

II. Hypermagnesemia:▪ **Clinical Features:**

- Bradycardia
- Hypotension
- Reduced consciousness
- Respiratory depression

▪ **Causes:**

- Acute and chronic renal failure
- Adrenocortical insufficiency
- Increased intake:
 - Antacids
 - Laxatives
 - Parenteral therapy

R_x**Treatment:**

- Restrict magnesium intake
- Promote renal Mg excretion with IV hydration and a loop diuretic
- Calcium gluconate may be used to reverse overt cardiac effects
- Dialysis in refractory cases.

Disorders of Acid – Base Balance

- Arterial blood pH is closely regulated in health to 7.4 by various mechanisms.
- The key principle for interpretation and diagnosis of acid-base disorders is that:
 - Primary changes in HCO_3 are = Metabolic
 - Primary changes in CO_2 are = Respiratory
 - Acidosis is a process that increases $[\text{H}^+]$, and therefore decreases pH.
 - Alkalosis is a process that decreases $[\text{H}^+]$, and therefore increases pH.
 - Compensation:
 - Compensation for metabolic acidosis is respiratory alkalosis (hyperventilation)
 - Compensation for metabolic alkalosis is respiratory acidosis (hypoventilation)
 - For respiratory acidosis, it is metabolic alkalosis by renal retention of HCO_3 .
 - For respiratory alkalosis, it is metabolic acidosis by renal excretion of HCO_3 .
 - Compensation never fully corrects pH; if pH is normal, consider a mixed disorder.
- Normal Values:
 - pH = 7.4
 - CO_2 = 40 (33 – 45 mmHg)
 - HCO_3 = 24 (22 – 28 mmHg)

Primary Alterations in HCO_3 (22–28 mEq/L):

I. Metabolic Acidosis (MA):

- It occurs when an acid other than carbonic acid accumulates in the body, resulting in decreased HCO_3 .
- Pathogenesis:
 - Serum $\text{HCO}_3 < 22$ mEq/L.
 - Compensation is respiratory alkalosis (hyperventilation) causing decreased PCO_2 .
 - Therefore = pH decreased, HCO_3 markedly decreased, PCO_2 decreased.
- The Anion Gap (AG):
 - It estimates unmeasured plasma anions (e.g. phosphate, ketones, lactate)

- It is calculated by $[\text{Na} + \text{K}] - [\text{Cl} + \text{HCO}_3]$
- It normally ranges from 10 – 18 mmol/l (avg. 15mmol/l)
- **Metabolic Acidosis with Increased AG:**
 - It results from increased production, or reduced excretion of organic acids.
 - Lactic acidosis
 - Ketoacidosis
 - Renal failure
 - Salicylate poisoning
 - Ethylene glycol poisoning
 - Methanol poisoning
- **Metabolic Acidosis with Normal AG:**
 - It results from loss of HCO_3 , or ingestion of H^+ ions.
 - Renal tubular acidosis
 - Diarrhea
 - Addison's disease
 - Pancreatic fistula
 - Drugs (e.g. acetazolamide)
 - Ammonium chloride ingestion
- **Management:**
 - Identify and correct the underlying cause.
 - IV fluids to correct associated sodium and water depletion.



Clinical Pearl:

Winter's Formula:

- It calculates expected compensation of PaCO_2 in metabolic acidosis.
- It therefore differentiates compensation or presence of a mixed disorder.
- Winter's formula = $\text{PaCO}_2 = (1.5 \times \text{HCO}_3) + 8 \pm 2$
- If CO_2 is within expected range, then it is a single disorder i.e. MA with compensation.
- If CO_2 is higher than expected, then it is a mixed disorder i.e. MA + respiratory acidosis.
- If CO_2 is lower than expected, then it is a mixed disorder i.e. MA + respiratory alkalosis

II. Metabolic Alkalosis:

- It is characterized by an increase in plasma bicarbonate concentration and plasma pH.
- **Pathogenesis:**
 - Serum $\text{HCO}_3^- > 28 \text{ mEq/L}$.
 - Compensation is respiratory acidosis (hypoventilation) causing increased PCO_2 .
 - Therefore = pH increased, HCO_3^- markedly increased, PCO_2 increased
 - Expected compensation $\text{PaCO}_2 = 0.7 \times (\text{measured } \text{HCO}_3^- - 24) \pm 2$
 - If PaCO_2 is within the expected range, it is a single disorder.
 - If PaCO_2 is not within the expected range, it is a mixed disorder.
- **Causes:**
 - Saline – Responsive (i.e. urinary $\text{Cl}^- < 20 \text{ mEq/L}$):
 - Vomiting
 - Villous adenoma
 - NG suction
 - Laxatives
 - Post-hypercapnia
 - Saline – Resistant (i.e. urinary $\text{Cl}^- > 20 \text{ mEq/L}$):
 - With Hypertension:
 - Primary hyperaldosteronism
 - Secondary hyperaldosteronism
 - Liddle's syndrome
 - With Normo- or Hypotension:
 - Barter's syndrome
 - Hypomagnesemia
 - Diuretic abuse

Primary Alterations in PCO_2 (33–45 mEq/L):

I. Respiratory Acidosis:

- **Pathogenesis:**
 - It is due to alveolar hypoventilation with retention of CO_2 .
 - $\text{PaCO}_2 > 45 \text{ mmHg}$.
 - Therefore, pH is decreased, HCO_3^- increased, PCO_2 markedly increased.
 - Metabolic alkalosis is compensation.

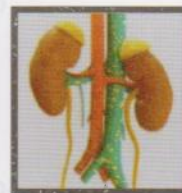
- Acute respiratory acidosis = HCO_3^- increases by 1 for every 10 the CO_2 increases
 - Chronic respiratory acidosis = HCO_3^- increases by 3.5 for every 10 the CO_2 increases.
 - If CO_2 is higher than predicted, there is a mixed acidotic process.
 - If CO_2 is lower than predicted, there is a mixed alkalotic process.
- **Causes:**
- CNS depression (e.g. sedatives, CNS trauma)
 - Neuromuscular disorders (e.g. myasthenia gravis, GBS, poliomyelitis)
 - Upper airway abnormalities (e.g. acute airway obstruction, obstructive sleep apnea)
 - Lower airway abnormalities (e.g. asthma, COPD)
 - Lung parenchyma abnormalities (e.g. pneumonia, restrictive lung disease)
 - Thoracic cage abnormalities (e.g. pneumothorax, flail chest)

I. Respiratory Alkalosis:

- **Pathogenesis:**
- It is due to alveolar hyperventilation with elimination of CO_2 .
 - $\text{PaCO}_2 < 33 \text{ mmHg}$.
 - Therefore, pH is increased, HCO_3^- decreased, PCO_2 markedly decreased.
 - Metabolic acidosis is compensation.
 - Acute respiratory alkalosis = HCO_3^- increases by 2 for every 10 the CO_2 increases
 - Chronic respiratory alkalosis = HCO_3^- increases by 5 for every 10 the CO_2 increase
 - If CO_2 is higher than predicted, there is a mixed acidotic process.
 - If CO_2 is lower than predicted, there is a mixed alkalotic process.
- **Causes:**
- CNS respiratory center overstimulation:
 - Anxiety
 - High altitude
 - Pregnancy
 - Shock
 - Cirrhosis
 - Others:
 - Congestive heart failure
 - Pulmonary embolism
 - Drugs e.g. salicylates
 - Sepsis

Chapter 4

NEPHROLOGY



Acute Renal Failure (Acute Kidney Injury)

Acute Kidney Injury (AKI):

▪ Definitions:

- Acute kidney injury (AKI) can be defined as:
 - Abrupt (i.e. < 48 hours) increase in creatinine ≥ 0.3 mg/dL, OR
 - Abrupt (i.e. < 48 hours) increase in creatinine of $\geq 50\%$. OR
 - Urine output of < 0.5 mL/kg/hour for > 6 hours.

▪ Types:

- Pre-renal failure
- Intrinsic renal failure
- Post-renal failure

▪ Workup for AKI:

- History and physical examination
- Urine evaluation:
 - Urine output
 - Urinalysis
 - Urine sediments
 - Electrolytes and osmolality
- Fractional Excretion of Sodium (FENa):
 - It is urine sodium/plasma sodium \div urine creatinine/plasma creatinine.
 - If < 1% it suggests pre-renal AKI.
 - If > 2% it suggests acute tubular necrosis.
 - In clinical practice, urine sodium and FENa gives the same information, for example in pre-renal azotemia:
 - Urine sodium (UNa) = < 20%
 - FENa = < 1 %



- Renal Ultrasound:
 - It is done to rule out obstruction.
 - It also evaluates the size of kidney to estimate chronicity of kidney disease.
- Other Workups:
 - Serologies – in glomerulonephritis
 - Renal biopsy – if cause remains unclear.

I. Pre-Renal AKI:

- It is the most common cause of AKI.
- It is potentially reversible.
- **(i). Causes:**
- Decreased effective arterial volume:
 - Hypovolemia
 - Congestive heart failure
 - Sepsis (systemic vasodilation)
- Local Causes:
 - Renal artery stenosis
 - Renal vasoconstriction:
 - NSAIDs
 - ACEI and ARBs
 - Contrast agents
 - Hepato-renal syndrome

(ii). Diagnosis & Management:

- **Laboratory Findings:**
 - Casts = hyaline casts
 - BUN: Creatinine ratio = > 20: 1
 - FENa = < 1 %
 - Urine sodium = < 20 mmol/l
 - Urine osmolality = > 500 mOsm/kg.

R_x

Management:

- Establish and correct the underlying cause.
- If hypovolemia is present restore blood volume as rapidly as possible.
- Monitoring of central venous pressure or pulmonary wedge pressure may aid in determining the rate of administration of fluids.
- Inotropic agents in critically ill patients.
- Correct metabolic acidosis by:
 - Restoration of blood volume
 - Sodium bicarbonate in severe cases.

II. Intrinsic Renal Failure (Renal AKI):

(i). Causes:

- Acute tubular necrosis (ATN) – most common cause
- Acute interstitial nephritis (AIN)
- Glomerulonephritis
- Contrast-induced acute kidney injury
- Rhabdomyolysis
- Small vessel disease, such as:
 - Cholesterol emboli
 - Thrombotic microangiopathy

(ii). Acute Tubular Necrosis (ATN):

- It is the most common cause of intrinsic renal failure.
- It is defined as kidney injury from ischemia and toxins resulting in sloughing off of tubular cells into the urine.
- It results in loss of sodium and water reabsorptive mechanisms due to loss of tubular cells, causing excretion of dilute urine (i.e. low urine osmolality).

▪ **Causes:**

- Ischemia – progression of pre-renal disease.
- Toxins:
 - Drugs = aminoglycosides, amphotericin, cisplatin
 - Pigments = hemoglobin, myoglobin
 - Proteins = immunoglobulin light chains
 - Crystals = uric acid, acyclovir, methotrexate

▪ **Clinical Course:**

- Initiation Phase:

- It lasts for about 36 hours.
- Slight decline in urine output, with rise in BUN.
- Maintenance Phase:
 - Oliguria (urine output < 400 – 500 mL/day) with raised BUN.
 - Hyperkalemia and metabolic acidosis.
- Recovery Phase:
 - Rise in urine volume.
 - Hypokalemia and increased vulnerability to infection.
- **Laboratory Findings:**
 - Casts = granular “muddy brown” casts
 - BUN: Creatinine ratio = < 20: 1
 - FENa = > 2 %
 - Urine sodium = > 20 mmol/l
 - Urine osmolality = < 300 mOsm/kg.

(iii). Acute Interstitial Nephritis (AIN):

- It is a form of intrinsic renal failure that damages tubules on an idiosyncratic (idiopathic) basis.
- It is characterized by antibodies and eosinophils attacking the cells lining the tubules.
- **Causes:**
 - Drugs – most common cause:
 - Penicillins & cephalosporins
 - Sulfa drugs (e.g. furosemide, thiazide diuretics)
 - Phenytoin; Rifampin,
 - Quinolones; Allopurinol
 - Infections = pyelonephritis,
 - Infiltrative = sarcoidosis, lymphoma, leukemia
 - Autoimmune = Sjogren’s, SLE
- **Clinical Course:**
 - Look for acute renal failure (rising BUN and creatinine) with:
 - Fever
 - Rash
 - Arthralgias
 - Eosinophilia and eosinophiluria
- **Laboratory Findings:**
 - Casts = RBCs, WBCs, WBC casts, eosinophils
 - BUN: Creatinine ratio = < 20: 1
 - FENa = cannot help in diagnosis
 - Urine sodium = cannot help in diagnosis
 - Urine osmolality = cannot help in diagnosis

(iv).

R_x**Management of Intrinsic Renal Failure:****General Measures:**

- Establish and correct the underlying cause.
- Correct volume depletion with intravenous fluid.
- If patient is septic, obtain blood cultures and start empiric antibiotics.
- Adjust doses of renally excreted drugs.
- **Corticosteroids accelerate recovery in acute interstitial nephritis (AIN)**

Treatment of Complications:

- Hyperkalemia:
 - Calcium gluconate – it is the first step (it is cardio-protective)
 - Insulin + glucose (temporarily shifts potassium into the cells)
 - Beta agonist (e.g. salbutamol nebulizer) – promotes cellular reuptake of K.
 - Kayexalate (sodium polystyrene sulfonate) – to remove K from body.
- Pulmonary Edema:
 - Sit up, and give high-flow oxygen by face mask.
 - Venous vasodilator (e.g. morphine)
 - Furosemide
 - If no response, urgent hemodialysis is necessary
 - Consider continuous positive airway pressure (CPAP) ventilation.
- Active Bleeding:
 - Fresh frozen plasma and platelets as needed.
 - Blood transfusion to maintain Hb > 10 g/dL and hematocrit > 30%.
 - Desmopressin to increase factor VIII activity and normalize bleeding time.

Acute Dialysis:

- Urgent dialysis is performed when condition is refractory to conventional therapy.
- **Urgent dialysis is indicated in following conditions:**
 - Metabolic acidosis (refractory)
 - Hyperkalemia ($K > 7$ mmol/L)
 - Volume overload (i.e. refractory pulmonary edema)
 - Uremic encephalopathy
 - Uremic pericarditis

III. Post-Renal AKI:

- It is the least common cause of acute kidney injury
- It is caused by obstruction of urinary tract.

I. Causes:

- Bladder Neck:
 - Benign prostatic hyperplasia
 - Prostate carcinoma
 - Anti-cholinergic drugs
- Bilateral Ureteral:
 - Malignancy
 - Retroperitoneal fibrosis
 - Ureteral stones

II. Diagnosis & Management:

- It presents with BUN: creatinine ratio is $> 20:1$ with patient having:
 - Distended bladder
 - Massive diuresis with catheter placement
 - Bilateral or unilateral hydronephrosis on renal ultrasound.
- Treatment:
 - Urinary catheter placement to decompress the bladder.
 - Urology consultation should be considered.

Types of Acute Renal Failure (Azotemia)

Variable	Pre-renal Azotemia	Renal Azotemia
BUN: Cr	$> 20:1$	$< 20:1$
Urine Na	$< 20 \text{ mEq/L}$	$> 20 \text{ mEq/L}$
FENa	$< 1\%$	$> 1\%$
Urine osmolality	$> 500 \text{ mOsm/kg}$	$< 300 \text{ mOsm/kg}$

Microscopic Urine Examination in Acute Kidney Injury

<u>Urine Sediment</u>	<u>Etiology</u>	<u>Classification</u>
Hyaline Casts	Dehydration	Pre-renal failure
Red cell casts	Glomerulonephritis	Intrinsic renal failure
Dysmorphic cells	Glomerulonephritis	Intrinsic renal failure
Granular "muddy-brown" cast	Acute tubular necrosis (ATN)	Intrinsic renal failure
White cells, eosinophils	Acute interstitial nephritis (AIN)	Intrinsic renal failure
White cells, white cell casts	Pyelonephritis	Intrinsic + Post-renal

Stages of CKD

<u>Stage</u>	<u>GFR (ml/min)</u>	<u>Description</u>
1	> 90	Normal
2	60–89	Mild CKD
3A	45–59	Moderate CKD
3B	30–44	Moderate CKD
4	15–29	Severe CKD
5	< 15 or on dialysis	Kidney failure (end-stage renal disease)

II. Causes

- Diabetes mellitus – most common cause
- Hypertension
- Glomerular diseases
- Interstitial kidney diseases
- Systemic inflammatory diseases (e.g. SLE)
- Renal artery stenosis
- Congenital and inherited diseases
- Idiopathic

Chronic Kidney Disease (CKD)

I. Introduction:

- **"CKD"** – refers to an irreversible deterioration in renal function.
- **"End-stage renal disease (ESRD)"** – refers to CKD that is so severe in which death is likely without renal replacement therapy (i.e. dialysis and renal transplantation).
- ESRD is defined as loss of renal function leading to a collection of symptoms and laboratory abnormalities that is referred to as "Uremia".
- **"Uremia"** is defined as presence of (same as for conditions which require dialysis):
 - Metabolic acidosis
 - Fluid overload (pulmonary edema)
 - Hyperkalemia
 - Uremic encephalopathy
 - Uremic pericarditis

Stages of CKD

<u>Stage</u>	<u>GFR (mL/min)</u>	<u>Description</u>
1	> 90	Normal
2	60 – 89	Mild CKD
3A	45 – 59	Moderate CKD
3B	30 – 44	Moderate CKD
4	15 – 29	Severe CKD
5	< 15 or on dialysis	Kidney failure (end-stage renal disease)

II. Causes:

- **Diabetes mellitus** – most common cause
- Hypertension
- Glomerular diseases
- Interstitial kidney diseases
- Systemic inflammatory diseases (e.g. SLE)
- Renal artery stenosis
- Congenital and inherited diseases
- Idiopathic

III. Clinical Manifestations:▪ **Anemia:**

- It is due to loss of erythropoietin.
- It results in normochromic normocytic anemia.

▪ **Bleeding:**

- Platelets are normal in number, but they don't degranulate.
- Platelets are therefore not able to release the contents of its granules.

▪ **Cardiovascular:**

- **Cardiovascular disease is the most common cause of death in CKD.**
- Cardiovascular disease manifests in the form of:
 - Pericarditis; Accelerated atherosclerosis
 - Hypertension; Hyperlipidemia; Volume overload, CHF.

▪ **Hypocalcemia:**

- Kidney transforms cholecalciferol into its active metabolite, 1, 25-dihydroxycholecalciferol, by the enzyme 1α -hydroxylase.
- In the absence of 1, 25-dihydroxy cholecalciferol the body will not absorb enough calcium from the gut resulting in hypocalcemia.

▪ **Renal Osteodystrophy:**

- It is metabolic bone disease that consists of:
 - Osteomalacia
 - Hyperparathyroid bone disease (osteitis fibrosa).
 - Osteoporosis
 - Osteosclerosis:
- Mechanism:
 - Vitamin D deficiency (absence of 1α -hydroxylase) causes Osteomalacia.
 - Hypocalcemia leads to secondary hyperparathyroidism and high PTH levels remove calcium from bones, making them soft and weak.

▪ **Hyperphosphatemia:**

- Phosphate is normally excreted through the kidneys.
- High PTH levels release phosphate from bones, but the kidneys are unable to excrete it.

▪ **Infection:**

- Patients with CKD are susceptible to infections, because neutrophils cannot degranulate.
- Infection is the second most common cause of death in CKD after cardiovascular disease.

▪ **Acidosis:**

- Patients with CKD will have metabolic acidosis.
- Acidosis is associated with increased tissue catabolism and decreased protein synthesis.

▪ **Endocrine Complications:**

- Loss of libido
- Sexual dysfunction (erectile dysfunction in males)
- Half-life of insulin is prolonged – insulin requirements may decline in diabetic patients.
- Relative insulin resistance and reduced appetite.

IV. Investigations:

- CBC, UCE,
- BUN and creatinine
- Urinalysis and quantification of proteinuria
- Calcium, phosphate, and PTH
- Albumin
- Blood glucose, HbA1C
- ECG (if patient is > 40 years or hyperkalemic)
- Renal ultrasound:
 - Small kidneys = chronic disease
 - Asymmetrical kidneys = renovascular or developmental disease

V. Management:

▪ **General Measures:**

- Smoking cessation
- Moderate protein restriction
- Low-sodium (if hypertensive)
- Restrict potassium (if oliguric or hyperkalemic)
- Restrict phosphate and magnesium

▪ **Blood Pressure:**

- Maximal Target:

- Non-diabetics = < 130/80 mmHg.
- Diabetics = < 125/75 mmHg.
- Agents:
 - Start with ACE inhibitor or ARBs, in both diabetics and non-diabetics.
 - ACEI may be effective and safe in advanced (stage 4 +) non-diabetic CKD.

<u>Condition</u>	<u>Treatment</u>
Anemia	Erythropoietin replacement and iron supplementation
Hypocalcemia	Vitamin D and calcium replacement
Osteomalacia	Vitamin D and calcium replacement
Bleeding	Desmopressin (DDAVP) increases platelet function; use only when bleeding
Hyperphosphatemia	Oral phosphate binders (see below)
Hypermagnesemia	Restriction of high-magnesium foods
Pruritis	Dialysis and ultraviolet light
Atherosclerosis	Dialysis
Endocrinopathy	Dialysis; estrogen and testosterone replacement
Metabolic acidosis	Sodium bicarbonate to keep $\text{HCO}_3^- > 22$ mmol/L.

▪ **Hyperphosphatemia:**

- Oral phosphate binders prevent phosphate absorption from the bowel.
 - If PO_4 is raised and calcium is low = calcium acetate, calcium carbonate
 - If PO_4 is raised and calcium is high = sevelamer, lanthanum

VI. Renal Replacement Therapy (RRT):

- It refers to either dialysis or renal transplantation.
- It can be given by following methods:
 - Hemodialysis – most common method
 - Hemofiltration
 - Peritoneal dialysis
 - Renal transplantation
- RRT in acute renal failure is given in following conditions:
 - Metabolic acidosis
 - Hyperkalemia
 - Fluid overload (pulmonary edema)

- Uremic pericarditis
- Uremic encephalitis
- RRT in chronic kidney disease (CKD) is given in following conditions:
 - CKD stage 5:
 - It is end-stage renal disease (ESRD).
 - It is associated with GFR of $< 15 \text{ mL/min}$.
 - Preparation of patient for it should begin up to 12 months before the predicted date.
 - Preparation includes:
 - Psychological preparation.
 - Choice between different dialysis methods.
 - Referral for renal transplantation
 - Screening for hepatitis B, C, and HIV.

(i). Hemodialysis (HD):

- It is the standard blood purification therapy in ESRD.
- It is also used in the treatment of AKI.
- Routes – (access to circulation):
 - Arteriovenous Fistula (AVF)
 - Central venous catheter
 - Arteriovenous shunt (e.g. Scribner shunt)
- **Physiology:**
 - The patient's blood is pumped through a hemodialyser.
 - Hemodialyser allows bidirectional diffusion of solutes b/w blood & the dialysate across a semi-permeable membrane down a concentration gradient.
 - Fluid removal (Na + Water) is via negative trans-membrane pressure (TMP) gradient (i.e. ultrafiltration).
 - Solute removal is via trans-membrane concentration gradient & inversely proportional to the size of solute (removal of K, urea, & Cr is effective than PO_4).
- **CKD:**
 - In CKD, vascular access for HD is gained by forming AVF, usually in the forearm.
 - AVF can be formed, up to 1 year before dialysis is contemplated.
 - HD is done when AVF matures:

- Increased pressure transmitted from artery to vein causes distention & thickening of vein – “arterialization”.
- **This process of maturation takes about 4 – 6 weeks.**
- Large-bore needles can then be inserted into the vein to provide access for HD.
- Screening:
 - **All patients must be screened for Hepatitis B, C, and HIV.**
 - Since hepatitis B is more infectious than hepatitis C & HIV, all dialysis units should have segregation facilities for Hep. B positive patients.
- **AKI:**
 - HD can be used for AKI patients.
 - Duration of HD:
 - Initially gradually = 1–2 hours/day (risk of confusion & convulsions)
 - Then in stable patients = 2–3 hours/day – OR – 4–5 hours on alternate days
 - Route – large-bore, double-lumen catheter inserted into:
 - Femoral vein
 - Internal jugular vein
 - **Avoid Subclavian Vein:**
 - Risk of thrombosis & stenosis, which in return:
 - Jeopardizes formation of AVF in arm if patient needs chronic HD.
 - Anticoagulation:
 - **It is standard practice to anticoagulate patients with heparin.**
 - Heparin dose can be reduced if there is a bleeding risk.
 - Alternative Agent:
 - Epoprostenol
 - Carries risk of hypotension
 - Anticoagulation can be avoided in patient:
 - In patients requiring short-term HD
 - In patients with coagulopathy (abnormal clotting)
- **Complications:**
 - Hypotension
 - Arrhythmias

- Disequilibrium syndrome
- AVF site:
 - Thrombosis; Stenosis
 - Aneurysm; Steal syndrome

(ii). Hemofiltration:

- It is principally used in the treatment of AKI.
- **Physiology:**
 - Blood under pressure passes down one side of a semi-permeable membrane.
 - Allowing water and solutes to pass across the membrane via TMP gradient, filtrate is discarded.
 - Replacement fluid is infused (solute concentrations similar to plasma, except NO potassium, urea, creatinine, and phosphate).
- **Advantages & Disadvantages:**
 - Advantages:
 - Less hypotension than hemodialysis.
 - Better volume control than hemodialysis
 - Disadvantages:
 - Expensive and takes longer time.
 - No survival advantage over hemodialysis

(iii). Peritoneal Dialysis:

- It is principally used in the treatment of CKD.
- **Continuous Ambulatory Peritoneal Dialysis (CAPD):**
 - Permanent Silastic catheter is inserted into the peritoneal cavity.
 - Two liters of sterile, isotonic dialysis fluid are introduced and left in place for 4-6 hours.
 - Metabolic waste products diffuse from peritoneal capillaries into the dialysis fluid down a concentration gradient.
 - The fluid is then drained and fresh dialysis fluid introduced, in a continuous four-times-daily cycle.
- **Automated Peritoneal Dialysis (APD):**
 - It works in a similar way as CAPD.
 - However, it uses a cycler machine to enhance solute and fluid removal during the night, or with only a single exchange to perform, during the day.

- **Advantages& Complications:**

- Advantages:

- It is simple to perform, less costly, and performed at home.
 - It is particularly useful in children and in elderly patients with cardiovascular instability.

- Complications:

- **Peritonitis – most commonly by staphylococcus aureus**
 - Catheter exit site infection
 - Catheter malfunction
 - Hernias and back pain

(iv). Renal Transplantation:

- It offers the best chance of long-term survival and complete rehabilitation.
- It is the most cost-effective treatment in patients with ESRD.
- Survival is best in living, HLA-identical, related donor (last 24 years on average)

- **Contraindications:**

- Absolute:

- Active malignancy
 - Active vasculitis
 - Severe heart disease
 - Severe occlusive aorto-iliac vascular disease.

- Relative:

- Age (< 1 year or > 75 years)
 - High risk of disease recurrence in the transplant kidney
 - Disease of lower urinary tract
 - Significant comorbidity

Glomerulonephritis & Nephritic Syndrome

Introduction:

▪ Definitions:

- Pathologically glomerulonephritis is defined as intra-glomerular inflammation ranging from focal proliferative to diffuse proliferative to crescentic
- Clinically glomerulonephritis presents with features that are collectively termed as **"Nephritic Syndrome"** - (mnemonic: HOPE)
 - Hematuria:
 - Dysmorphic RBCs,
 - RBCs and RBC casts – key finding in the urine.
 - Hypertension
 - Oliguria
 - Proteinuria (< 3.5 g/day)
 - Edema

▪ Causes:

- ANCA positive Vasculitis:
 - Wegener's granulomatosis
 - Microscopic polyangiitis
 - Churg – Strauss syndrome
- Anti – Glomerular Basement Membrane (GBM) Disease:
 - Goodpasture's syndrome
 - Anti-GBM disease
- Immune – Complex Diseases:
 - Renal Limited Diseases:
 - Post-streptococcal glomerulonephritis
 - Membranoproliferative glomerulonephritis
 - IgA nephropathy
 - Rapidly progressive glomerulonephritis
 - Systemic Diseases:
 - SLE
 - Cryoglobulinemia

- Subacute bacterial endocarditis
- Henoch – Schonlein purpura

Glomerulonephritis:

I. Post-Streptococcal Glomerulonephritis:

- It is the most common type of post-infectious glomerulonephritis.
- **Clinical Features:**
 - It occurs 1-4 weeks after a sore-throat caused by Group A β -hemolytic streptococci i.e. streptococcus pyogenes.
 - It frequently occurs in children 6-10 years of age.
 - Sudden onset of fever, nausea, oliguria and hematuria (cocoa-colored urine)
 - Lab findings:
 - ASO titers = Elevated
 - Serum C3 = Decreased
- **Renal Biopsy:**
 - Light Microscopy:
 - Hypercellular & enlarged glomeruli
 - Leukocytic infiltration, lumpy-bumpy appearance.
 - Electron Microscopy = subepithelial humps
 - Fluorescence Microscopy = granular appearance
- **Treatment:**
 - Supportive; 95% of cases resolve spontaneously.
 - Antibiotics; diuretics

II. IgA Nephropathy:

- It is also known as Berger Disease.
- It is the **most common** cause of nephritic syndrome.
- **Association:**
 - Henoch-Schonlein Purpura
 - Increased frequency of disease in patients with:
 - Celiac disease
 - Liver disease
- **Clinical Features:**
 - Most common age group = older children and young adults.

- It presents with recurrent episodes of hematuria (gross or microscopic).
- It occurs after upper respiratory infection, gastrointestinal, or urinary tract infection.



Clinical Pearl:

Glomerulonephritis:

- **Post-streptococcal glomerulonephritis:**
 - Occurs 1 – 2 weeks after infection.
 - Complement levels (C3) are low.
- **IgA nephropathy:**
 - Occurs 1 – 2 days after infection.
 - Complement levels (C3) are normal.

▪ **Diagnosis:**

- IgA levels are increased only in 50% of cases.
- Renal biopsy is the most accurate test.
 - Light Microscopy = Mesangial widening and proliferation.
 - Electron Microscopy = Mesangial electron-dense deposits.
 - Fluorescence Microscopy = Granular appearance

▪ **Treatment:**

- There is no treatment to reverse the disease.
- Chronic renal failure occurs in 15 – 40% of cases over a period of 20 years.
- Severe proteinuria is treated with ACE inhibitors and steroids

III. Goodpasture's Syndrome:

- It is a type-II hypersensitivity disease. It is a male-dominant.
- It is caused by anti-basement membrane antibodies against collagen in glomerular and pulmonary capillaries.
- It begins with hemoptysis and ends with renal failure.
- **Clinical Features:**
 - Hemoptysis, dyspnea and possible respiratory failure.
 - Unlike Wegener's granulomatosis, there is:
 - NO upper respiratory tract involvement (e.g. sinusitis)
 - NO skin involvement
 - NO gastrointestinal involvement

▪ **Diagnosis:**

- Anti-glomerular basement membrane antibodies – best initial test
- Kidney biopsy – most accurate test
- Anemia is often present from chronic blood loss from hemoptysis
- CXR may show pulmonary infiltrates.

▪ **Treatment:**

- Plasma exchange;
- Immunosuppressive therapy with corticosteroids and cyclophosphamide;
- Renal transplantation.

IV. Wegener's Granulomatosis:

- It is necrotizing medium-sized and small vessel vasculitis involving upper respiratory tract, lung and renal vessels.
- Males > Females.
- Age = 40 – 60 years
- Marker of disease = elevated serum c-ANCA in 95%.

▪ **Clinical features:**

- Upper Respiratory:
 - Sinusitis; Otitis media
 - Rhinitis, nasal mucosal ulceration, saddle-nose deformity
- Lower Respiratory:
 - Pulmonary infiltrate; pulmonary hemorrhage, pleurisy
 - Hemoptysis, nodular lesions on chest x-ray.
- Renal:
 - Hematuria
 - Red cells and red cell casts on microscopic examination of urine

▪ **Diagnosis:**

- Presence of c-ANCA
- Renal biopsy:
 - Focal necrotizing glomerulonephritis (mild form)
 - Crescentic glomerulonephritis (severe form)

V. Alport Syndrome:

- It is hereditary glomerulonephritis that progress to chronic renal failure.
- **Pathogenesis:**
 - Trait: X-linked recessive (most common); autosomal dominant; autosomal recessive.
 - It is caused by defective GBM synthesis due to abnormal collagen type IV.
- **Clinical Features:**
 - Gross or microscopic hematuria (most common presenting sign).
 - Age for the onset of symptoms = 5 – 20 years.
 - Age for overt renal failure = 20 – 50 years (men)
 - Family history of renal failure.
 - Nerve deafness
 - Eye disorders:
 - Lens dislocation
 - Posterior cataracts
 - Corneal dystrophy.
- **Renal Biopsy:**
 - Electron Microscopy:
 - “Basket & Weave” appearance of GBM i.e.:
 - Areas of GBM thinning alternating with areas of thickening.



Clinical Pearl:

Glomerulonephritis with Low Serum Complements:

1. Post-streptococcal glomerulonephritis
2. Subacute bacterial endocarditis
3. SLE
4. Cryoglobulinemia
5. Membranoproliferative glomerulonephritis type-II

Nephrotic Syndrome

Introduction:

▪ Definition:

- It is a glomerular syndrome characterized by:
 - Massive proteinuria (daily loss of $\geq 3.5\text{gm}$)
 - Hypoalbuminemia (plasma albumin $< 3\text{ gm/dL}$)
 - Generalized edema
 - Hyperlipidemia and lipiduria

▪ Causes:

- Primary Glomerular Diseases:
 - Minimal change disease
 - Membranous glomerulopathy
 - Membranoproliferative glomerulonephritis
 - Focal segmental glomerulosclerosis
- Systemic Diseases:
 - Diabetes mellitus
 - SLE
 - Amyloidosis
 - Cryoglobulinemia

▪ Workup:

- Best initial test is urinalysis.
- Renal biopsy is the most accurate test.
- Urinalysis is not sufficiently accurate in estimating urinary protein loss.
- Proteinuria can be estimated by:
 - 24 – hour urinary protein
 - Urine albumin: creatinine ratio:
 - It is more accurate and easier than 24 hour protein collection.
 - Ratio of 2 means 2 grams of protein excreted over 24 hours.
 - Ratio of 3 means 3 grams of protein excreted over 24 hours, and so on.

▪ Treatment:

- General Measures:
 - Protein supplementation
 - Diuretics for edema

- Treat hyperlipidemia with statins
- Sodium restriction
- Specific Measures:
 - ACE inhibitors or ARBs = decrease proteinuria; slows progression of disease
 - Primary glomerular diseases = steroids ± immunosuppressive therapy
 - Secondary glomerular diseases = treat the underlying cause
 - Treatment of complications such as:
 - Infections = antibiotics
 - Thromboembolism = anticoagulation

Individual Diseases:

I. Minimal Change Disease:

- It is also known as Lipid Nephrosis.
- **It is the most common cause of nephrotic syndrome in children.**
- It is due to cytokine mediated mechanism that causes GBM to lose its negative charge.
- **Associations:**
 - Respiratory infections
 - Immunization
 - Atopic disorders (eczema, rhinitis)
 - Hodgkin disease
 - NSAIDS
- **Difference from Other Nephrotic syndromes:**
 - Highly selective proteinuria (albumin, not globulins)
 - No hypertension
 - No progression to renal failure
 - **Excellent response to corticosteroids**
- **Morphology:**
 - Light microscopy = No change.
 - Fluorescence microscopy = No change (no immunoglobulin; no complements)
 - Electron Microscopy = visceral epithelial cells show diffuse effacement of foot processes.

II. Membranous Glomerulopathy:

- It is the most common cause of nephrotic syndrome in adults
- It is a form of chronic immune complex-mediated disease.
- **Causes:**
 - Idiopathic 85%
 - Drugs (captopril, gold, Penicillamine)
 - Autoimmune (SLE, thyroiditis)
 - Infections (hepatitis B and C, syphilis, malaria)
 - Malignancy (lung cancer, colon cancer, melanoma)
- **Features:**
 - Non- selective proteinuria (loss of albumin and globulin)
 - Hypertension
 - Progression to renal failure 10% within 10 years.
 - Not good response to corticosteroids
- **Renal Biopsy:**
 - Electron Microscopy:
 - Sub-epithelial deposits (between GBM and overlying epithelial cells).
 - **Spike & Dome** appearance of membrane on silver stains.

III. Focal Segmental Glomerulosclerosis:

- It is characterized by sclerosis of some glomeruli, and in these affected glomeruli, only a portion of capillary tuft is involved.
- **Causes:**
 - Idiopathic
 - HIV nephropathy
 - Heroin addiction
 - Sickle cell disease
 - Massive obesity
- **Difference from Minimal Change Disease:**
 - Non- selective proteinuria
 - Hypertension
 - Progression to renal failure 50% within 10 years.
 - Poor response to corticosteroids
- **Clinical Features:**
 - The typical patient is a young male with uncontrolled hypertension
 - Microscopic hematuria

- Renal biopsy shows sclerosis in capillary tufts.

IV. Membranoproliferative Glomerulonephritis:

- It is a glomerular disease in which the principal mode of presentation is the nephrotic syndrome.
- **Types:**
 - Type-I MPGN:
 - It results from the activation both classic and alternative complement pathway.
 - It is the most common type.
 - It is associated with hepatitis B, C, and cryoglobulinemia, SLE and Subacute bacterial endocarditis.
 - Type-II MPGN:
 - It results from activation of only alternative complement pathway.
 - It is also known as “**dense-deposit disease**”, or “alternative MPGN”.
 - It is associated with **C3 nephritic factor**, which is an auto-antibody that prevents degradation of C3-convertase causing sustained activation of C3, resulting in very low C3 levels.
- **Renal Biopsy:**
 - Light Microscopy = Tram Track appearance i.e. double layered basement membrane
 - Electron Microscopy:
 - MPGN-I = **Sub-endothelial deposits.**
 - MPGN-II: = **Intra-membranous deposits.**

V. Renal Amyloidosis:

- Amyloidosis refers to accumulation of insoluble fibrillar proteins that form β -pleated sheaths.
- **Clinical Features:**
 - Patients may have:
 - Multiple myeloma
 - Waldenstrom's macroglobulinemia
 - Chronic inflammatory diseases:
 - Inflammatory bowel disease
 - Rheumatoid arthritis
 - Tuberculosis

▪ **Renal Biopsy:**

- Nodular glomerulosclerosis.
- Electron Microscopy = amyloid fibrils, "Apple – Green" birefringence with Congo red stain.

▪ **Treatment:**

- Treat the underlying disease.
- Prednisone + Melphalan, is the combination of choice.
- Bone marrow transplantation may be used for multiple myeloma

Urinary Tract Infections (UTI)

Introduction:

▪ Definitions:

(i). Anatomic Definitions:

- Lower UTI = urethritis (inflammation of urethra); cystitis (inflammation of bladder).
- Upper UTI = pyelonephritis (inflammation of renal parenchyma); prostatitis (inflammation of prostate)

(ii). Clinical Definitions:

- Uncomplicated UTI = lower UTI in immunocompetent non-pregnant women without underlying structural or neurologic disease.
- Complicated UTI:
 - Upper UTI in non-pregnant women
 - Any UTI (upper or lower) in pregnant women
 - Any UTI (upper or lower) in men
 - UTI with underlying structural disease or immunosuppression

(iii). Laboratory Definitions:

- Bacteriuria = presence of bacteria in urine
- UTI = presence of a pure growth of $> 10^5$ organisms per mL of fresh mid-stream urine sample

▪ Microbiology:

- **E. coli – most common overall cause of UTI**
- Uncomplicated UTI = E. coli, Proteus, Klebsiella,
- Complicated UTI = E. coli, Pseudomonas, Enterococci
- Catheter-associated = Yeast, E. coli, Staphylococcus epidermidis
- Urethritis = Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma

▪ Clinical Features:

- Urethritis:
 - Urethral discharge, NO fever
 - Dysuria, urgency, frequency, \pm hematuria
- Cystitis:
 - NO urethral discharge, NO fever

- Dysuria, urgency, frequency, hematuria, change in urine color, with supra-pubic pain.
- Pyelonephritis:
 - Classic triad of high-grade fever with chills, loin pain & tenderness over kidneys
 - Nausea, vomiting, and diarrhea.
- Renal Abscess:
 - It presents in manner identical to pyelonephritis, except that:
 - It has persistent fever despite appropriate antibiotics.
- Prostatitis:
 - Chronic Prostatitis:
 - NO fever, dysuria, urgency, frequency (like cystitis),
 - Symptoms of obstruction, such as hesitancy, dribbling, poor stream
 - Acute Prostatitis:
 - Fever, perineal pain,
 - Tenderness of digital rectal examination.

II. Investigations:

- **Urine dipstick/Urinalysis:**
 - Pyuria (presence of WBCs) + Bacteriuria
 - Increased leukocyte esterase = a marker of WBCs
 - Increased nitrites = a marker of bacteria
 - With or without hematuria
- **Urine Culture:**
 - Urine culture is gold standard investigation
 - Urine is cultured from fresh midstream urinary (MSU).
 - UTI = presence of a pure growth of $> 10^5$ organisms per mL of fresh MSU.
 - Asymptomatic Bacteriuria = presence of $> 10^5$ organisms per mL in the urine of apparently healthy asymptomatic individuals.
 - Asymptomatic Bacteriuria warrants treatment:
 - Pregnant women
 - Infants
 - In those with urinary tract abnormalities

- **Sterile Pyuria** = presence of WBCs in urine with negative urine culture ($< 10^5$ organisms).
- Sterile Pyuria is a feature of:
 - Renal tuberculosis – most common
 - Treated UTI < 2 weeks prior
 - Inadequately treated UTI
 - Calculi; prostatitis
 - Bladder tumor; Polycystic kidney
- **Other Investigations:**
 - CBC, UCE, electrolytes
 - Blood cultures (if febrile and possibly complicated UTI)
 - DNA detection in high-risk patients for:
 - Chlamydia trachomatis
 - Neisseria gonorrhoeae
 - Renal tract ultrasound or CT scan in:
 - Children
 - Men
 - Women with recurrent infections
 - Recurrent UTIs in men warrants urologic workup i.e.:
 - Renal ultrasound
 - Intravenous urography
 - Abdominal CT scan
 - Voiding cystography

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Treatment:

- **General Measures:**
 - Fluid intake of at least 2 L per day.
 - Urinary alkalinizing agent such as potassium citrate.
 - Cranberry juice
- **Lower UTI:**
 - Uncomplicated Lower UTI (Cystitis & Urethritis):
 - Treatment duration is 3 days in women and 10 days in men.
 - Trimethoprim-sulfamethoxazole (TMP-SMX) is the best initial treatment.
 - Second-line choices are:

- Amoxicillin
 - Nitrofurantoin
 - Cephalexin (1st-generation cephalosporin)
 - Ciprofloxacin
- Urethritis:
 - Treat for both Neisseria and Chlamydia in high-risk patients:
 - Neisseria = ceftriaxone is the antibiotic of choice
 - Chlamydia = doxycycline or azithromycin
- Complicated Lower UTI:
 - Treatment duration is for 10 – 14 days.
 - Agents of choice are:
 - Fluroquinolones e.g. ciprofloxacin
 - Co – amoxiclav
- Pregnancy:
 - **Any Bacteriuria (symptomatic or asymptomatic) should be treated during pregnancy.**
 - Urine culture should be repeated at each menstrual cycle.
 - Drugs of choice:
 - Cephalexin (first-generation cephalosporin)
 - Amoxicillin
 - Nitrofurantoin
 - Drugs that are contraindicated are:
 - Trimethoprim-sulfamethoxazole (TMP-SMX)
 - Fluroquinolones (ciprofloxacin)
 - Tetracycline
- **Pyelonephritis:**
 - Mild Cases:
 - Treatment duration is 10 days.
 - Fluroquinolones (ciprofloxacin) – are first line therapy.
 - Severe Cases:
 - Severe cases mean:
 - With associated systemic toxicity
 - Pregnant patients
 - Severe nausea and vomiting

- Suspected bacteremia
 - Admit the patient, and start intravenous antibiotics for 7 – 14 days.
 - Change intravenous drugs to oral form when patient improved clinically and afebrile after 24 – 48 hours and then complete 14 day course.
 - Options are:
 - Cefuroxime (2nd generation cephalosporin)
 - Ceftriaxone (3rd generation cephalosporin)
 - Gentamicin (aminoglycoside)
 - Co – amoxiclav (ampicillin– sulbactam)
- **Prostatitis:**
 - Acute prostatitis:
 - Treatment duration is 28 days.
 - Treatment options are ciprofloxacin and TMP-SMX.
 - Chronic prostatitis:
 - Treatment duration is 6 – 12 weeks.
 - Treatment options are ciprofloxacin and TMP-SMX

Urinary Tract Calculi

I. Introduction:

- Urinary calculi (stones) consist of aggregates of crystals containing small amounts of proteins and glycoprotein.
- Nephrocalcinosis refers to calcification within renal parenchyma from calcium deposition.
- It affects men more than women; with peak age at onset is between 20 and 30 years.
- **Risk Factors:**
 - Low fluid intake
 - Diet: high protein, high sodium, low calcium
 - Hypercalcemia of any cause
 - Renal tubular acidosis type I
 - Ileal disease (increase oxalate absorption and urinary excretion)
 - Inherited conditions (e.g. medullary sponge kidney, cystinuria)

II. Types of Stones:

(i). Calcium oxalate & phosphate:

- They are the most common renal stones. (calcium oxalate > calcium phosphate)
- Appearance = irregular, with sharp projections.
- Calcium oxalate is the most common type in adults.
- Calcium phosphate is the most common type in children.
- They are radio-opaque.
- Urine characteristics:
 - Increased calcium, oxalate, urate and pH,
 - Decreased citrate and volume.
- Causes:
 - Secondary Hypercalciuria:
 - Primary hyperparathyroidism
 - Type 1 renal tubular acidosis
 - Sarcoidosis
 - Secondary Hyperoxaluria:
 - Crohn's disease
 - Ileal disease with intact colon
 - Gastric bypass

(ii). Magnesium ammonium phosphate:

- They form the largest renal stones.
- They are also called "struvite" or "staghorn calculi".
- Appearance = smooth and dirty white.
- They are formed by urea-splitting bacteria (proteus) which converts urea to ammonia. This alkaline urine causes precipitation of magnesium ammonium phosphate salts.
- Urine characteristics:
 - Increased ammonia (NH₃)
 - Increased pH > 7 (alkaline urine)

(iii). Uric acid:

- Appearance = hard, smooth, often multiple.
- They are radio-lucent on plain film.
- Urine characteristics:
 - Increased uric acid (e.g. gout)
 - Decreased pH (e.g. from chronic diarrhea)

(iv). Cystine:

- Appearance = hexagonal, translucent, white crystals.
- It is due to genetic defect in renal reabsorption of amino acids, resulting in cystinuria.
- It forms at low urinary pH.

III. Clinical Features & Management:

Clinical Features:

- It is unilateral in about 80% of cases.
- It may present with gross or microscopic hematuria.
- It presents with renal colic typically with ureteric obstruction:
 - Acute loin pain
 - Pain radiates anteriorly and often to the groin.
 - Pain is so severe that the patient cannot stay still
 - Fever usually absent.

Diagnosis:

- Abdominal X-ray:
 - 90% of stones contain calcium and are seen on X-ray.
 - Uric acid stones are radiolucent and non-visible.
- Intravenous urography (IVU) – most commonly used investigation
- **Non-contrast spiral CT scan – most accurate investigation**

- Other Investigations:
 - Urinalysis
 - Urine culture
 - UCE, BUN: Cr, electrolytes, PO₄, PTH, uric acid.

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Acute Treatment:

- Bed rest and application of warmth to the site of pain.
- Strong analgesics:
 - Narcotics (e.g. morphine, pethidine)
 - Diclofenac
- 90% of stones < 4 mm in diameter will pass spontaneously.
- 10% of stones > 6 mm in diameter will pass spontaneously and the rest will require endoscopic surgical removal.
- Indications for immediate urologic evaluation and hospitalization:
 - Urinary tract obstruction
 - Urosepsis (i.e. severe infection)
 - Intractable pain or vomiting
 - Acute renal failure
- Urologic Treatment:
 - Percutaneous nephrostomy – is indicated when:
 - Patent has obstructive anuria
 - Pyonephrosis (severe infection)
 - Extracorporeal shockwave lithotripsy (ESWL)
 - It is the most common method.
 - It is best for stones > 5mm, but < 2 cm in diameter.
 - Percutaneous nephrolithotomy it is best for stones > 2 cm.
 - Open surgery – rarely performed these days.

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Chronic Treatment:

- Increase fluid intake to at least 2 L/day.
- Increase calcium intake:
 - Calcium forms an insoluble salt with dietary oxalate.
 - Lowering oxalate absorption and excretion.
- Avoid:
 - Sodium intake
 - Foods that are rich in oxalate (spinach, rhubarb)
 - High-protein diet; only moderate protein
 - Vitamin D supplementation
 - Vitamin C supplementation
- Thiazide diuretics reduce urinary calcium and are useful in:
 - Recurrent stone-formers
 - Patients with hypercalciuria
- Uric acid stone = urinary alkalinization (potassium citrate), allopurinol
- Magnesium ammonium phosphate = antibiotics to treat UTI, urologic intervention
- Cystine = urine alkalinization, Penicillamine, Tiopronin, Captopril

Renal Tubular Acidosis (RTA)

I. Proximal RTA (Type-II):

- It is characterized by decreased proximal tubular reabsorption of HCO_3 .
- It is because renal threshold for reclaiming HCO_3 is lowered from normal 24 mEq/L to 15 mEq/L.
- **Features:**
 - Urinary pH is initially > 5.5 due to loss of filtered HCO_3 in urine.
 - When serum HCO_3 is equal to renal threshold, the proximal tubules reclaim HCO_3 causing the urine pH to drop to < 5.5
 - Hypokalemia is common.
- **Causes:**
 - Idiopathic
 - Fanconi's syndrome (i.e. decreased reabsorption of HCO_3 , PO_4 , glucose, amino acids).
 - Multiple myeloma
 - Amyloidosis
 - Drugs (e.g. acetazolamide, heavy metals)
 - Renal transplant
- **Diagnosis & Management:**
 - Diagnosis:
 - IV sodium bicarbonate load.
 - There is high fractional excretion of bicarbonate ($> 15\%$)
 - Treatment:
 - High doses of bicarbonate.
 - Thiazide diuretics – these produce volume depletion, which increases the renal threshold for reclaiming HCO_3 .

II. Distal RTA (Type-I):

- It is due to inability to excrete H^+ and generate acidic urine in the distal tubule, even in states of metabolic acidosis.
- **Features:**
 - Rickets or Osteomalacia
 - Nephrocalcinosis with renal calculi
 - Alkaline urine (i.e. urinary pH > 5.5)

▪ **Causes:**

- Idiopathic
- Genetic (e.g. Marfan's, Ehlers-Danlos syndrome)
- Autoimmune (e.g. SLE, Sjogren's)
- Nephrocalcinosis (e.g. hypercalcemia, medullary sponge kidney)
- Tubule-interstitial disease (e.g. chronic pyelonephritis, chronic interstitial nephritis)
- Drugs (e.g. lithium, amphotericin)

▪ **Diagnosis & Management:**

- Diagnosis:
 - Acid load i.e. oral ammonium chloride load is given.
 - There is failure to lower urine pH < 5.5
- Management = oral administration of sodium bicarbonate.

III. Type-IV RTA:

- It is due to Hyporeninemic Hypoaldosteronism.
- It results from destruction of juxtaglomerular (JG) apparatus.
- Hypoaldosteronism causes hyperkalemia and acidosis.

▪ **Causes:**

- Diabetic nephropathy
- Tubulointerstitial disease (e.g. sickle cell, SLE, amyloidosis)
- Drugs:
 - Decrease renin (e.g. NSAIDs)
 - Decrease aldosterone synthesis (e.g. ACEI, ARBs, heparin)
 - Decrease response to aldosterone (e.g. K-sparing diuretics, trimethoprim-sulfamethoxazole)

▪ **Treatment:**

- Treat the underlying cause.
- For hyperkalemia:
 - Fludrocortisone, OR
 - Furosemide

Renal Tubular Acidosis (RTA)

Variable	Proximal (Type-II)	Distal (Type-I)	Type-IV
Defect	HCO ₃ reabsorption	H ⁺ secretion	Aldosterone deficiency/resistance
Serum K ⁺	Low	Low	High
Urinary pH	Initially > 5.5; then < 5.5 once serum is acidic	> 5.5	< 5.5
Treatment	Thiazides, large doses of bicarbonate	Replace bicarbonate	Furosemide, fludrocortisone
Complications	–	Nephrolithiasis	Hyperkalemia

APKD & RCC

Adult Polycystic Kidney Disease (APKD):

I. Introduction:

- It is an autosomal dominant disease (prevalence 1: 1000)
- It is characterized by formation of small cysts in both kidneys, lined by tubular epithelium starting from infancy.
- The cysts enlarge and gradually compress & damage the surrounding normal kidney.
- **Genetics:**
 - PKD1 Mutation:
 - It accounts for 85% of cases.
 - ESRD develops in about 50% of cases with early onset (~52 years)
 - PKD2 Mutation:
 - It accounts for 15% of cases.
 - ESRD develops in minority of patients with late onset (~69 years)
- **Clinical Features:**
 - Abdominal pain
 - Bilateral, palpable kidneys
 - Hematuria – with little or no proteinuria
 - Renal failure
 - Associations:
 - Hypertension - start after the age of 20.
 - UTI
 - Berry aneurysm (subarachnoid hemorrhage in 10%)
 - Hepatic cysts – 30%
 - Aortic regurgitation, Mitral regurgitation
 - Colonic diverticula
 - Abdominal wall hernia

II. Diagnosis & Management:

- **Diagnosis:**
 - US:
 - It is the best initial test & screening investigation of choice.
 - It demonstrates cysts in 95% of patients over the age of 20.
 - MRI is the most accurate test.

- Molecular diagnosis – mutation screening of PKD1 & PKD2
- MRI angiography:
 - It is done to detect intracranial aneurysm.
 - It can be done in families with history of subarachnoid hemorrhage.
- **Treatment:**
 - Blood Pressure Control:
 - It is important because CV morbidity & mortality are common in renal disease.
 - There is no evidence that control of moderate HTN slows development of ESRD.
 - Tolvaptan:
 - It is a vasopressin V2 receptor antagonist.
 - It can slow cyst formation in some patients.
 - Renal Replacement Therapy:
 - Dialysis
 - Renal transplantation

Renal Cell Carcinoma (RCC):

I. Introduction:

- It is the most common tumor of the kidney in adults.
- It arises from renal tubular cells (adenocarcinoma).
- **Histologic Types:**
 - Clear cell carcinoma:
 - It is the most common type – 85%.
 - It is associated with early spread of tumor into renal pelvis – hematuria.
 - Papillary carcinoma
 - Chromophobe carcinoma
 - Collecting duct carcinoma
- **Clinical Features:**
 - Incidental finding if asymptomatic.
 - Symptomatic:
 - Hematuria – 60%
 - Loin pain – 40%

- Mass – 25%.
 - Classic triad of pain, mass, & hematuria – 10% cases
- Associated Features:
 - Fever
 - Raised ESR
 - Polycythemia – tumor secretion of erythropoietin
 - Hypercalcemia – tumor secretion of PTHrP

II. Diagnosis & Management:

- **Diagnosis:**
 - US:
 - It is the best initial test.
 - It allows differentiation b/w solid tumor & simple renal cyst.
 - Contrast-Enhanced CT Abdomen & Chest:
 - It is the best next step once US shows features suggestive of a tumor.
 - It is combined with CT-chest for staging purposes.
- **Management:**
 - Resectable Tumors:
 - Radical nephrectomy is the treatment of choice.
 - It involves removal of kidney, peri-renal fascia, & ipsilateral para-aortic nodes.
 - It can be done laparoscopically as well as open surgery.
 - Partial nephrectomy is recommended for tumors ≤ 4 cm.
 - Metastatic Tumors:
 - It is resistant to most chemotherapeutic agents.
 - Mainstay of Therapy:
 - Tyrosine-kinase inhibitors – Sunitinib, Pazopanib
 - Mammalian target Rapamycin (mTOR) inhibitors – Temsirolimus, Everolimus.

Diseases of Prostate Gland

I. Benign Prostatic Hyperplasia (BPH):

- It is characterized by stromal and glandular proliferation resulting in prostatic hyperplasia.
- It is a very common disorder in men over 50 years of age.
- It is not considered to be a premalignant lesion.
- Most common site = periurethral (transitional) zone.
- **Pathogenesis:**
 - DHT:
 - DHT (dihydrotestosterone) is the primary mediator.
 - DHT is synthesized from testosterone by 5 α -reductase.
 - It causes stromal and glandular proliferation.
 - Estrogen:
 - It is the co-mediator of the disease.
 - It increases the synthesis of androgen receptors.
 - It thus renders cells more susceptible to the action of DHT.
- **Clinical Course:**
 - Obstructive Symptoms:
 - These are primary symptoms and are specific of BPH
 - These symptoms include hesitancy, poor stream, and sensation of incomplete emptying.
 - Irritative Symptoms:
 - These are secondary symptoms and are NOT specific of BPH:
 - These symptoms include urinary frequency, urgency of micturition, and urge incontinence.
 - Acute Retention:
 - Sudden onset of inability to micturate.
 - Associated with painful distention of bladder.
 - Chronic Retention:
 - Gradual, slowly progressive inability to micturate.
 - Associated with painless distention of bladder.
- **Complications:**
 - Post-renal azotemia
 - Bilateral hydronephrosis
 - Bladder hypertrophy and trabeculation

- Bladder diverticulum (due to increased pressure)
- Prostatic infarcts

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Treatment:

- Medical Treatment:
 - Prostate < 30 g = alpha blockers (tamsulosin)
 - Prostate > 30 g = 5 α -reductase inhibitors (finasteride) \pm alpha-blocker
- Surgical Treatment:
 - TURP (transurethral resection of prostate) – Gold Standard treatment
 - Open prostatectomy

II. Prostatic Adenocarcinoma:

- It is the most common form of cancer in men, and the second leading cause of cancer death.
- It is typically a disease of men over age 50.
- **Risk factors:**
 - Aging – most important risk factor
 - Family history
 - Race
 - Increased fat consumption
 - Decreased vitamins A and E, selenium and soy products.
- **Site:**
 - **Peripheral zone** (70%)
 - Palpable on rectal examination.
- **Metastasis:**
 - Local = seminal vesicle
 - Hematogenous = bone (lumber spine)
 - The finding of osteoblastic metastasis in bone is diagnostic of this cancer in men.
 - Lymphatic spread = obturator nodes
- **Staging:**
 - T1 = Cancer found incidentally

- T2 = Cancer is confined within prostate.
- T3a = extra-prostatic extension with seminal vesicle invasion.
- T3b = extra-prostatic extension without seminal vesicle invasion.
- T4 = direct invasion of contiguous organs.
- N0 = no spread to lymph nodes.
- N1 = spread to lymph nodes

▪ **Clinical Course:**

- Early stage:
 - Asymptomatic.
 - Because it arises peripherally away from urethra.
- Advanced stage:
 - Nocturia & dysuria, dribbling
 - Difficulty in starting and stopping urine
 - Hematuria
 - Back pain – bone metastasis
 - Weight loss

▪ **Prostate-specific Antigen (PSA):**

- It is of great value in assessing the response to therapy.
- It decreases after prostatectomy or radiotherapy.
- If the value remains high after therapy, it indicates recurrence or dissemination.
- It is organ specific, but not cancer specific and is increased in following conditions:
 - Cancer (highest values)
 - BPH
 - Prostatitis
 - Infarcts
 - Ejaculation

PSA Density:

- It is the ratio between serum PSA and volume of prostate gland.
- It increases with aging, because the size of gland increases.
- It has therefore, age-specific upper reference values:
 - 2.5 ng/mL for men = 40 – 49 years
 - 3.5 ng/mL for men = 50 – 59 years
 - 4.5 ng/mL for men = 60 – 69 years
 - 6.5 ng/mL for men = 70 – 79 years

PSA Velocity:

- PSA velocity is the rate of change of PSA values with time.
- PSA velocity of 0.75 ng/mL/year distinguishes men with and without cancer.

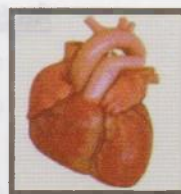
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Treatment:

- Localized cancer = Radical prostatectomy
- Advanced cancer = External beam radiotherapy
- Metastatic cancer = Endocrine therapy:
 - Androgen receptor antagonists = Cyproterone Acetate
 - Gonadotrophin-releasing hormone (GnRH) analogue = Goserelin
 - Orchiectomy (removal testes to decrease testosterone production)

Chapter 5

CARDIOLOGY



Electrocardiogram (ECG)

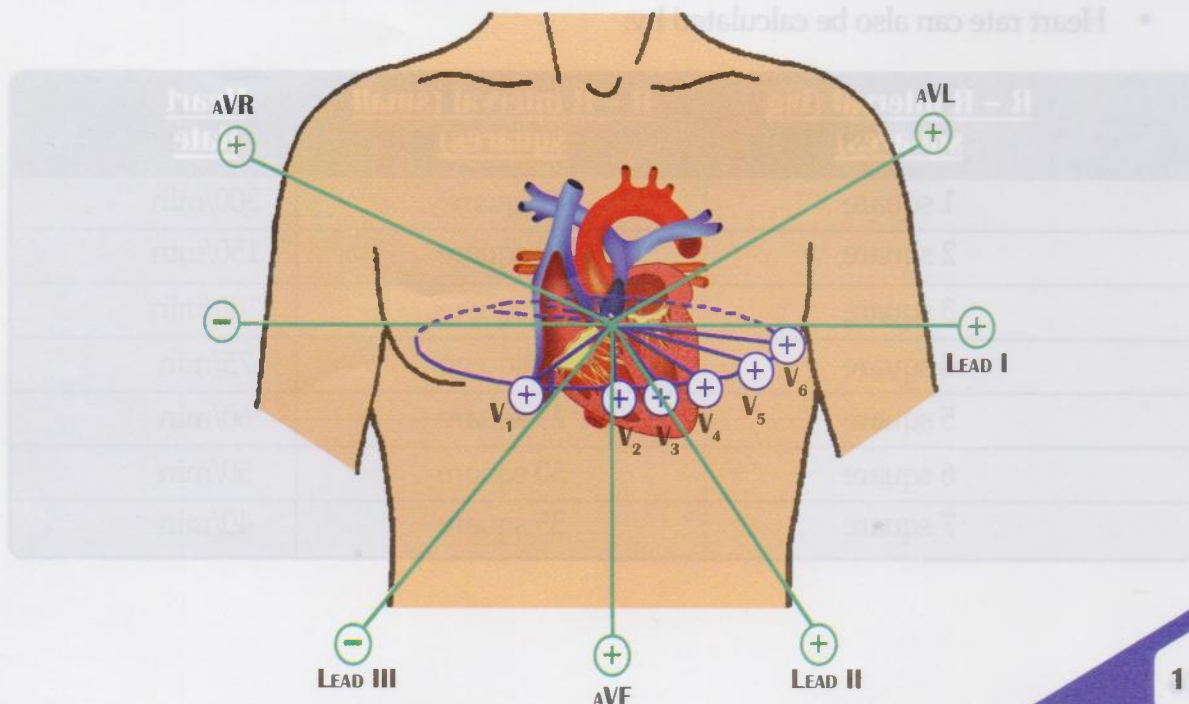
The Standard 12 – Lead ECG:

I. Lead Placement:

- ECG is a graphical representation of the electrical activity of the heart.
- 12-lead ECG is one in which 12 different electrical signals are recorded at approximately the same time
- 12-lead ECG consists of 3 limb leads, 3 augmented leads, and 6 chest leads.

Limb Leads:

- These are bipolar leads.
- Lead I = records signal b/w right (-ve) and left (+ve) arm.
- Lead II = records signal b/w right arm (-ve) and left leg (+ve).
- Lead III = records signal b/w left arm (-ve) and left leg (+ve).



▪ **Augmented Leads:**

- These are unipolar leads.
- aVL = records signal b/w left arm (+ve) and a central terminal (-ve) formed by combining right arm and left leg electrodes.
- aVR = records signal b/w right arm (+ve) and a central terminal (-ve) formed by combining left arm and left leg electrodes.
- aVF = records signal b/w left leg (+ve) and a central terminal (-ve) formed by combining right arm and left arm electrodes.

▪ **Chest Leads:**

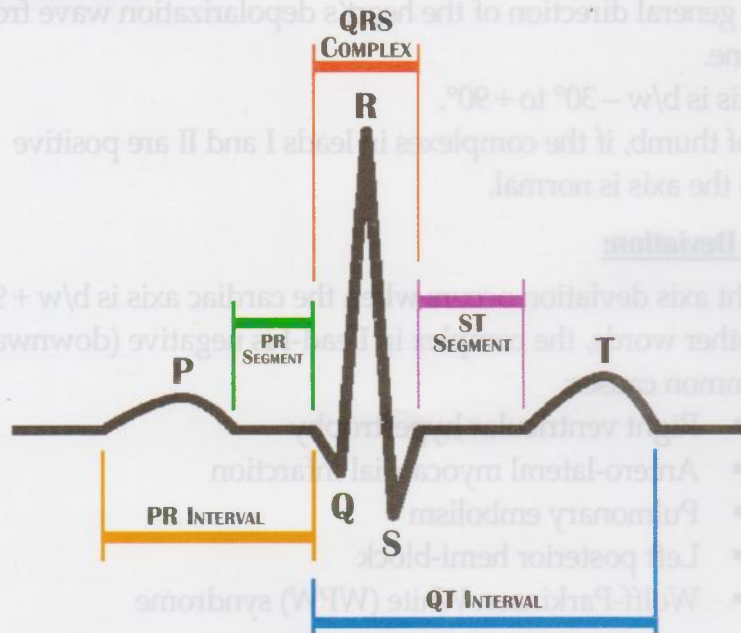
- These are unipolar leads (V1 – V6).
- V1 and V2 lie over the right ventricle.
- V3 and V4 lie over the interventricular septum.
- V5 and V6 lie over the left ventricle.
- These leads record the electrical activity of heart in a horizontal plane.

II. ECG Conventions:

- Sensitivity : 10 mm = 1mV
- Paper speed : 25 mm per second
- Each large (5mm) square : 0.2 seconds
- Each small (1mm) square : 0.04 seconds
- Heart rate interval. : divide 300 by the number of bigsquares b/w R-R interval.
- Heart rate : divide 1500 by the number of small squares b/w R-R interval.
- Heart rate can also be calculated by:

<u>R – R interval (big squares)</u>	<u>R – R interval (small squares)</u>	<u>Heart Rate</u>
1 square	5 square	300/min
2 square	10 square	150/min
3 square	15 square	100/min
4 square	20 square	75/min
5 square	25 square	60/min
6 square	30 square	50/min
7 square	35 square	40/min

III. Components of ECG:



- **P-wave:**
 - It indicates atrial depolarization.
 - It is tall in right atrial enlargement (P-pulmonale).
 - It is bifid in left atrial enlargement (P-mitrale).
- **PR Interval:**
 - It is normally 0.12 seconds i.e. 3 small squares.
 - It is the time interval from onset of atrial to ventricular depolarization.
 - **It is prolonged in conduction blocks.**
 - **It is shortened in WPW-syndrome**
- **QRS Complex:**
 - It indicates ventricular depolarization.
 - It is normally 0.12 seconds i.e. 3 small squares.
 - If > 0.12 seconds it means ventricular conduction problem.
- **ST-Segment:**
 - It connects QRS complex and the T-wave.
 - ST-segment elevation is seen in myocardial infarction, pericarditis and LV aneurysm.
 - ST-segment depression is seen in myocardial ischemia or infarction.
- **T-Waves:**
 - It indicates ventricular repolarization.
 - It is elevated in hyperkalemia, and hyperacute phase of MI.
 - It is inverted in hypokalemia and myocardial ischemia or infarction.

IV. Cardiac Axis:

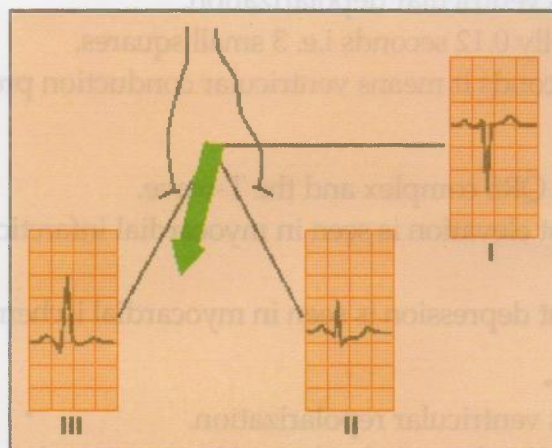
- It refers to general direction of the heart's depolarization wave front in the frontal plane.
- Normal axis is b/w -30° to $+90^{\circ}$.
- As a rule of thumb, if the complexes in leads I and II are positive (i.e. upward deflection) the axis is normal.

(i). Right Axis Deviation:

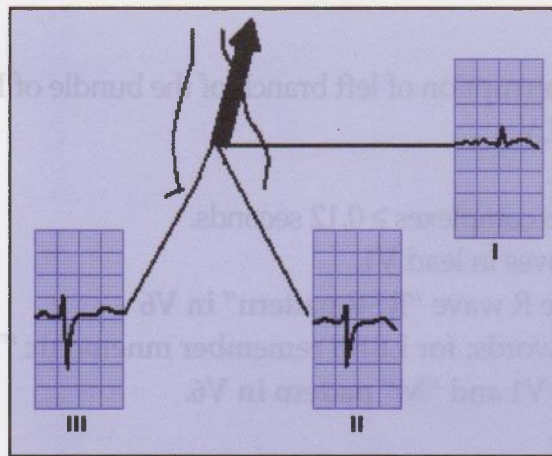
- Right axis deviation occurs when the cardiac axis is b/w $+90^{\circ}$ to $+180^{\circ}$.
- In other words, the complex in Lead-I is negative (downward deflection).
- Common causes:
 - Right ventricular hypertrophy
 - Antero-lateral myocardial infarction
 - Pulmonary embolism
 - Left posterior hemi-block
 - Wolff-Parkinson White (WPW) syndrome

(ii). Left Axis Deviation:

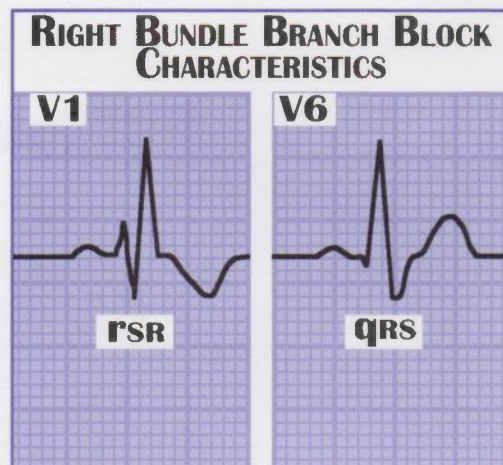
- Left axis deviation occurs when cardiac axis is b/w -30° to -90° .
- In other words, the complex in Leads-II and III are negative (downward deflection).
- Common causes:
 - Left ventricular hypertrophy
 - Inferior wall myocardial infarction
 - Ventricular tachycardia
 - Left anterior hemi-block
 - Wolff-Parkinson White (WPW) syndrome



Right Axis Deviation:

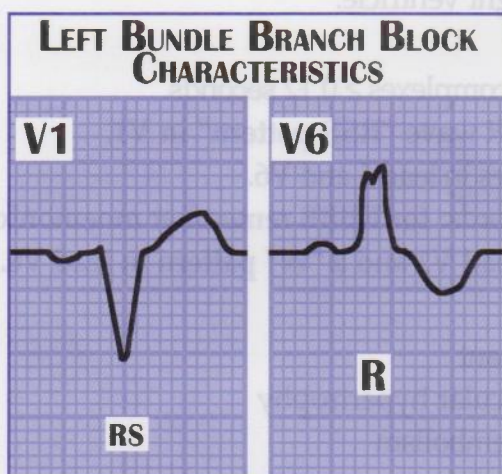
Left Axis Deviation:**V. Bundle Branch Block (BBB):****(i). Right BBB:**

- It results from interruption of right branch of the bundle of His, which delays activation of the right ventricle.
- Findings on ECG:
 - Broad QRS complexes ≥ 0.12 seconds.
 - Tall double R wave **"RSR pattern" in V1.**
 - Deep S waves in lead-I and V6.
 - In simple words: **for RBBB remember mnemonic "MaRRoW" i.e. an "M" pattern in lead V1 and a "W" pattern in lead V6.**
- Common Causes:
 - Normal variant
 - Right ventricular hypertrophy
 - Pulmonary embolism
 - Atrial septal defect
 - Coronary artery disease.



(ii). Left BBB:

- It results from interruption of left branch of the bundle of His, which delays activation of the LV.
- Findings on ECG:
 - Broad QRS complexes ≥ 0.12 seconds.
 - Deep S waves in lead V1.
 - Tall double R wave "RSR pattern" in V6
 - In simple words: for LBBB remember mnemonic "WiLLiaM" i.e. "W" pattern in V1 and "M" pattern in V6.
- Common Causes:
 - Coronary artery disease
 - Hypertension
 - Aortic valve disease
 - Cardiomyopathy



Arrhythmias

Bradycardia, Tachycardia, & Atrioventricular (AV) Blocks:

I. Sinus Bradycardia:

- It refers to a heart rate of < 60 beats per minute (bpm).
- It is called sinus, because each P-wave is followed by a QRS complex.
- Causes:
 - Myocardial infarction
 - Increased vagal tone (athletes, sleep, inferior wall MI)
 - Metabolic (hypothermia, hypothyroidism, hypoxia)
 - Raised intracranial pressure
 - Drugs (beta-blockers, calcium channel blockers, amiodarone)
 - Sick sinus syndrome

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Treatment:

- Asymptomatic = no treatment
- Symptomatic:
 - Best initial therapy = atropine
 - Most effective therapy = pacemaker

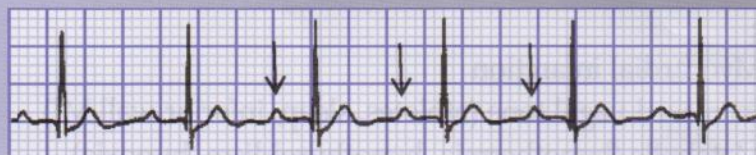
II. First-degree AV-Block:

- It is characterized by:
 - Prolonged PR-interval (>200ms or > 0.2 sec).
 - Each P-wave (arrow) is followed by a QRS complex (i.e. there are no missed beats).
- Causes:
 - AV-nodal disease
 - Increased vagal tone (athletes)
 - Acute inferior wall myocardial infarction
 - Electrolyte disturbances

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Treatment:

- Asymptomatic = no treatment
- Symptomatic:
 - Best initial therapy = atropine
 - Most effective therapy = pacemaker

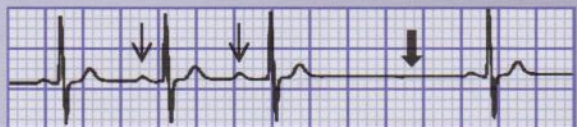



First-degree AV-block

III. Second-degree AV-Block:

- It is characterized by dropped beats, because some impulses from the atria fail to conduct to the ventricles.
- It is of two types; Mobitz type-I, and II.
- Mobitz type-II is more DANGEROUS than Mobitz Type-I.
- Mobitz type-II is associated with cardiac arrest and sudden cardiac death.

<u>Mobitz Type-I</u>	<u>Mobitz Type-II</u>
<u>Definition:</u> <ul style="list-style-type: none"> ▪ Also known as “Wenckebach’s phenomenon”. ▪ It is characterized by progressive lengthening of PR-interval until a dropped beat occurs, and the cycle is repeated. 	<u>Definition:</u> <ul style="list-style-type: none"> ▪ It is far more pathologic than Mobitz type-I. ▪ It is characterized by a dropped beat WITHOUT progressive lengthening of PR-interval.
<u>Pathology:</u> <ul style="list-style-type: none"> ▪ It is due to abnormal AV node due to: <ol style="list-style-type: none"> 1. Inferior wall MI 2. Myocarditis 3. Mitral valve surgery 4. High vagal tone (athletes) 	<u>Pathology:</u> <ul style="list-style-type: none"> ▪ It is due to abnormal Purkinje-His due to: <ol style="list-style-type: none"> 1. Anterior wall MI 2. Degeneration of conduction system 3. Infiltrative diseases (e.g. amyloidosis) 4. Aortic valve surgery
<u>Factors:</u> <ul style="list-style-type: none"> ▪ It worsens with carotid sinus massage. ▪ It improves with atropine. 	<u>Factors:</u> <ul style="list-style-type: none"> ▪ It improves with carotid sinus massage. ▪ It worsens with atropine.

<p>Treatment:</p> <ul style="list-style-type: none"> Asymptomatic = no treatment Symptomatic = atropine, followed by pacemaker 	<p>Treatment:</p> <ul style="list-style-type: none"> Asymptomatic = (permanent) pacemaker Symptomatic = (permanent) pacemaker
<p>ECG:</p>  <p>Arrow = P-wave; thick arrow = no P-wave (missed beat), note progressive lengthening of PR interval.</p>	<p>ECG:</p>  <p>PR interval is constant, but some P-waves (arrow) are not conducted (missed beat)</p>

IV. Third-degree (Complete) Heart Block:

- It is characterized by complete interruption of AV-conduction in which P-wave has no relationship to QRS complex.
- Causes:**
 - Myocardial infarction
 - Cardiomyopathy
 - Severe Hyperkalemia
 - Congenitally in infants of mothers having SLE.
 - Acute inflammation (e.g. aortic root abscess in infective endocarditis)
 - Chronic inflammation (e.g. Sarcoidosis, Chagas disease)
- Clinical Features:**
 - Syncope; dizziness
 - Acute heart failure
 - Cannon A-waves** (waves visible in neck due to large-volume pulse from compensatory increase in stroke volume).
 - Stokes-Adams attacks** (sudden loss of consciousness without warning due to episodes of ventricular asystole)



No relation between P-waves & QRS complex

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Treatment:

- Asymptomatic patients = pacemaker placement (permanent)
- Symptomatic patients = pacemaker placement (permanent)

V. Sick Sinus Syndrome (SSS):

- Also known as "Sinoatrial Disease".
- It is caused by fibrosis, degenerative changes, or ischemia of the SA node.
- It is most common in old people.
- It is a tachycardia-bradycardia syndrome presenting with palpitations and syncope.
- Common features:
 - Sinus bradycardia
 - SA block (sinus arrest)
 - Paroxysmal atrial tachycardia
 - Paroxysmal atrial fibrillation
 - AV block
- Treatment:
 - Symptomatic patients = permanent pacemaker
 - Atrial Pacing:
 - It prevents episodes of atrial fibrillation
 - It does not affect prognosis, therefore, not indicated in asymptomatic patients

VI. Sinus Tachycardia:

- It refers to a heart rate of > 100 beats per minute.
- It is called sinus, because each P-wave is followed by a QRS complex.
- Causes:
 - Anxiety; fever
 - Anemia; heart failure
 - Thyrotoxicosis; Pheochromocytoma
 - Drugs (e.g. Beta-agonists)

Treatment = treat the underlying cause.

Atrial Tachyarrhythmias:**I. Atrial Flutter:**

- It is characterized by a single large (macro) re-entry circuit, within the right atrium encircling the tricuspid annulus.
- The atrial rate is about 300 beats per minute.
- It should always be suspected when there is narrow-complex tachycardia of 150/minute.
- It is associated with 2:1, 3:1, or 4:1 AV block.
- It is usually asymptomatic, but can present with palpitations, syncope and lightheadedness.
- Diagnosis:
 - Carotid sinus pressure increases the degree of AV-block and reveals flutter waves.
 - Intravenous adenosine increases the degree of AV-block and reveals flutter waves.
 - ECG:
 - Regular rhythm** (unlike atrial fibrillation, which has irregular rhythm)
 - Saw-toothed flutter waves.** (Best seen on inferior leads i.e. II, III, aVF).
- Management = same as atrial fibrillation (see below)



Atrial Flutter: saw-toothed waves, regular QRS complexes

In A-Flutter
* 250-350 bpm

60-80 bpm

irritable

automaticity

* Backup Pacemakers

Foci

only fire when SA node sig not reaches AV node.



recurrent circuit.

refractory period.

For every P wave how many QRS complexes.

AV block

Backup mech. for preventing AV reg're

II. Atrial Fibrillation (AF):

- It is the most common sustained cardiac arrhythmia.
- It is characterized by multiple foci within the atria that fire continuously in a chaotic pattern, causing irregular atrial rhythm.
- **Diagnosis:**
 - Raised JVP without "a" wave.
 - Irregularly irregular pulse.
 - ECG:
 - No P-waves.
 - Normal, but irregular QRS complexes i.e. **irregularly irregular RR-intervals**.



- **Causes:** mnemonic: **PIRATES**
 - Pulmonary embolism
 - Ischemic heart disease (including MI)
 - Rheumatic heart disease
 - Atria myxoma
 - Thyrotoxicosis
 - Ethanol
 - Sepsis
 - Chronic AF:
 - Hypertension
 - CHF
- **Classification:**
 - Paroxysmal AF = intermittent, self-terminating
 - Persistent AF = sustained for >7 days, can be terminated by chemical or electrical cardioversion.
 - Permanent AF = typically > 1 year; and when cardioversion has failed.

R_x**Management of Acute AF:**

- Hemodynamically Unstable = immediate electrical cardioversion to sinus rhythm.
- Hemodynamically Stable:

STEP 1: Rate Control

- Target rate 60 – 100 bpm (if the rate is too rapid)
- Agents:
 - β -blockers (preferred agents)
 - Calcium channel blockers (verapamil, diltiazem)
 - Digoxin

○ **STEP 2: Rhythm Control**

- **AF < 48 hours & low risk of stroke using CHADS-VAS score (see below)**
 - Intravenous heparin followed by cardioversion
 - Electrical cardioversion is preferred over pharmacologic cardioversion.
 - Electrical cardioversion is also called DC cardioversion.
 - Pharmacologic cardioversion can be done by parenteral flecainide, procainamide and amiodarone.
- **AF > 48 hours & high risk of stroke using CHADS-VAS score (see below)**
 - If AF is > 48 hours then we can follow any one of the following two options:

Option – 1:

- Anticoagulate for 3 weeks, then perform cardioversion.
- Anticoagulate for 4 weeks after performing cardioversion.
- Anticoagulate with Warfarin.
- Target INR is 2 – 3.

Option – 2:

- To avoid waiting 3 weeks for anticoagulation, obtain trans-esophageal echocardiogram (TEE) to look for left atrial thrombus.
- If left atrium thrombus is present then follow option – 1, i.e. anticoagulation (3 weeks) – cardioversion – anticoagulation (4 weeks)
- If left atrium thrombus is absent then directly perform cardioversion without anticoagulation for 3 weeks.



Clinical Pearl: **Hemodynamic Instability:**

- Hemodynamic instability in almost all types of arrhythmias is an indication for cardioversion.
- Hemodynamic instability refers to:
 1. Hypotension
 2. Chest pain
 3. Dyspnea (congestive heart failure)
 4. Confusion,

▪ **Management of Chronic AF:**

- Rate control with beta blocker or calcium channel blocker.
- Anticoagulation with warfarin.
- **"Lone AF":**
 - It refers to AF in patients who are < 60 years old and without underlying heart disease or cardiovascular risk factors.
 - Patients with lone AF have low risk for embolization (stroke), therefore heparin or warfarin are not indicated, however, **aspirin can be used.**

▪ **CHA2DS2 – VASc Score:**

- It is scoring system used to assess the risk of thromboembolism in patients with atrial fibrillation.

<u>CHA2DS2-VASc Score</u>	
Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	2 points
Diabetes mellitus	1 point
Previous stroke (TIA)	2 points
Vascular disease	1 point
Age 65 – 74 years	1 point
Sex Category (female)	1 point
Maximum total score	9 points
Score 0 = aspirin only (lone AF)	
Score 1 = oral anticoagulation (warfarin) or aspirin	
Score ≥ 2 = warfarin	



Clinical Pearl:

Cardioversion & Defibrillation:

Cardioversion:

- It refers to delivery of shock that is in synchrony with QRS complexes.
- Objective is to TERMINATE dysrhythmias.
- Indications: AFib, Atrial flutter, 'SVT', ventricular tachycardia with a pulse.

Defibrillation:

- It refers to delivery of shock that is not in synchrony with QRS complexes.
- Objective is to CONVERT dysrhythmias to normal sinus rhythm.
- Indications: Ventricular fibrillation, VT without a pulse.

III. Multifocal Atrial Tachycardia (MAT):

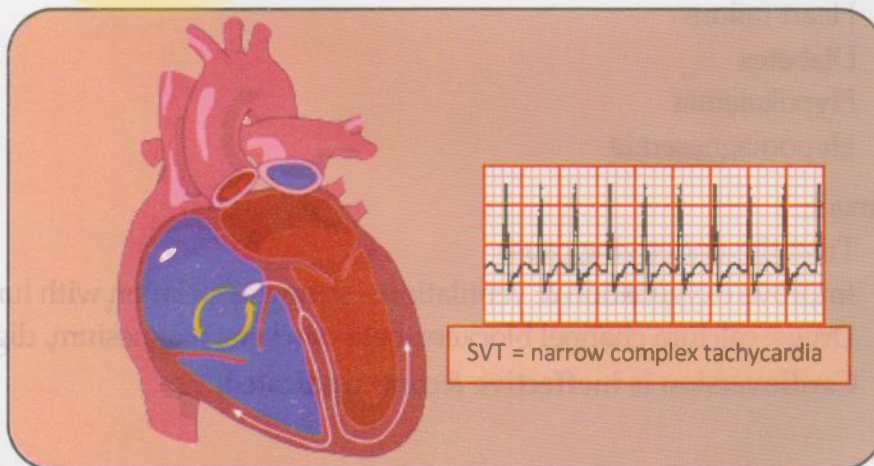
- It is an arrhythmia caused by multiple sites of competing atrial activity.
- It is characterized by irregular rate > 100 bpm.
- ECG:
 - **≥ 3 morphological distinct P-waves**
 - Irregular P-P intervals
 - Isoelectric baseline between the P-waves.
- Causes:
 - **Chronic pulmonary disease – most common cause**
 - Coronary artery disease
 - Valvular heart disease
 - Heart failure
 - Diabetes
 - Hypokalemia
 - Hypomagnesemia
- Treatment:
 - Treat the underlying cause
 - Improve oxygenation & ventilation – strong association with lung disease
 - Drugs: calcium channel blockers, beta-blockers, magnesium, digoxin
 - **Cardioversion is ineffective & contraindicated.**

Supraventricular Tachycardia (SVT):

- SVTs originate at or above the atrioventricular (AV) node. i.e. "above the bundle of His".
- Since conduction below the AV node (i.e. ventricles) is normal, SVTs have narrow QRS complex.
- SVTs occur mostly by two mechanisms:
 - Re-entry:
 - Re-entrant arrhythmias occur when an electrical impulse recurrently travels in a tight circle within the heart.
 - Automaticity:
 - Abnormal automaticity occurs when cardiac cells starting firing (action potential) spontaneously.

I. Atrioventricular Nodal Re-entrant Tachycardia (AVNRT):

- It is the most common cause of supraventricular tachycardia.
- It is characterized by **a re-entry circuit within the AV node** that depolarizes the atrium and ventricles nearly simultaneously.
- It has two pathways;
 - The inferior "slow" pathway for antegrade conduction i.e. from AV node to the ventricles.
 - The superior "fast" pathway for retrograde conduction i.e. re-entering the atria via the AV node.
- These two pathways have electrophysiological properties similar to AV nodal tissue.
- ECG:
 - Narrow complex tachycardia i.e. tachycardia with normal QRS complexes.
 - No discernible P-waves (i.e. P-waves are buried within QRS complexes because circuit is short and conduction is rapid)



II. Atrioventricular Reciprocating Tachycardia (AVRT):

- It is characterized by an accessory pathway between the atrium and ventricle that causes a re-entry circuit.
- The accessory pathway has electrophysiological properties similar to ventricular myocardium.
- This type of SVT is seen in Wolff-Parkinson-White (WPW) Syndrome.
- ECG:
 - Narrow complex tachycardia
 - P-waves may or may not be discernible.

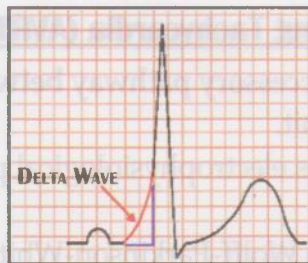
II.**R_x****Treatment of SVT**

- Treatment is not always necessary.
- Acute episode in hemodynamically unstable patient = DC cardioversion
- Acute episode in hemodynamically stable patient:
 - Best initial step is vagal maneuvers (carotid massage, Valsalva, ice immersion)
 - If vagal maneuvers fail then drug of choice is IV adenosine (3 – 12 mg).
 - If adenosine isn't effective then:
 - IV beta blockers (metoprolol)
 - IV calcium channel blockers (diltiazem, verapamil)
- Recurrent SVT:
 - Catheter ablation – the most effective therapy.
 - Alternative options – prophylaxis with beta-blockers, CCB, or flecainide.

III. Wolff-Parkinson-White (WPW) Syndrome:

- It is characterized by premature excitation of the ventricles due to an accessory pathway from the atria known as "Bundle of Kent".
- It is a type of AVRT supraventricular tachycardia.
- ECG:
 - Shortened PR – interval
 - Delta wave i.e. slurring of QRS complex
 - Widened QRS complexes





Types:

○ Sinus Rhythm:

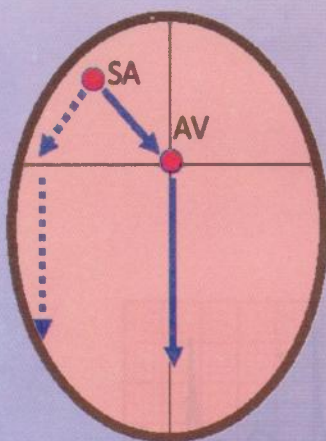
- The ventricles are depolarized through AV node and accessory pathway.
- It produces shortened PR interval, widened QRS complex, and delta wave.

○ Orthodromic Tachycardia:

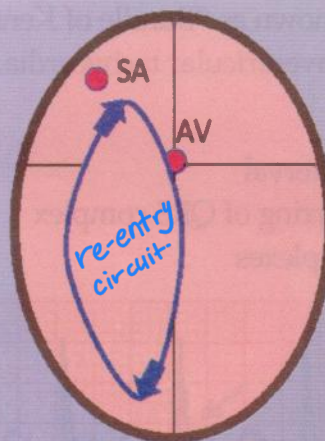
- **It is the most common form of tachycardia in WPW syndrome.**
- The re-entry circuit passes antegradely through the AV node and retrogradely through the accessory pathway.
- It produces a narrow QRS complex (no delta wave), because the ventricles are depolarized in a normal way.
- ① The resultant ECG is therefore, indistinguishable from other forms of SVT.

○ Pre-excitatory Atrial Fibrillation:

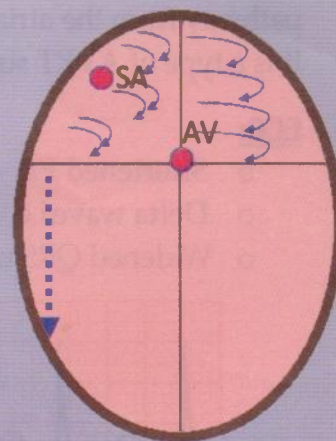
- The ventricles are largely depolarized through the accessory pathway.
- It produces irregular, broad-complex tachycardia.
- It is called pre-excitatory because it produces a dangerously rapid ventricular rate because accessory pathway lacks the rate-limiting properties of AV node.



Sinus Rhythm



Orthodromic Tachycardia



Atrial Fibrillation

R_x**Treatment:**

- Hemodynamically Unstable = DC Cardioversion.
- Acute case with arrhythmia (AFib):
 - Procainamide – drug of choice:
 - It is Class-I anti-arrhythmic agent (Na-channel blocker)
 - Alternative agents: Amiodarone, Quinidine
- Chronic Therapy:
 - **Radiofrequency ablation (RFA) is first line therapy in symptomatic patients.**
 - **RFA is nearly always curative.**
- Drugs to avoid:
 - Digoxin, and calcium channel blockers
 - They block the normal AV node and force conduction into the abnormal accessory pathway.

Clinical Pearl:**Types of Tachycardia:**

- **Narrow Complex Tachycardia:**
 - Arrhythmia originates at or above the level of AV node.
 - ECG = rate is > 100 bpm and QRS complex duration is < 120 ms (normal)
- **Broad Complex Tachycardia:**
 - Arrhythmia originates below AV node or outside of normal conducting system.
 - ECG = rate is > 100 bpm and QRS complex duration is > 120 ms (i.e. > 3 small square)

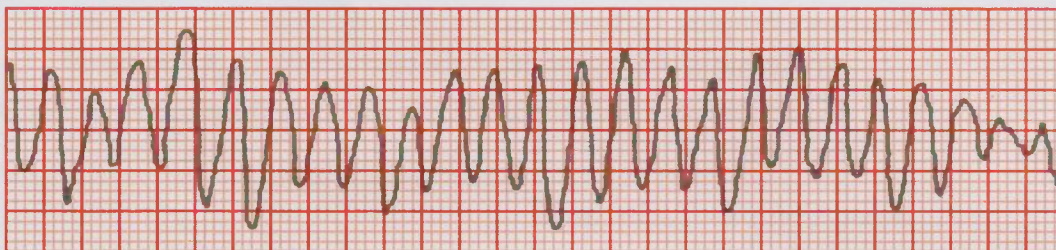
Pulselessness (Cardiac Arrest):

- It refers to sudden loss of pulse.
- Causes:
 - Shockable rhythm:
 - Ventricular fibrillation (VF)
 - (Pulseless) Ventricular tachycardia (VT)
 - Non-Shockable rhythm:
 - Asystole
 - Pulseless electrical activity (PEA)

Shockable Rhythms:

I. Ventricular Fibrillation (VF):

- It is characterized by multiple foci in the ventricles that fire rapidly, leading to a chaotic quivering of the ventricles and no cardiac output.
- It presents with syncope, absence of blood pressure, and pulselessness.
- Causes:
 - Ischemic heart disease – most common cause
 - Pre-excitation AFib in WPW syndrome.
- **ECG:**
 - No P-waves and no QRS complexes can be identified.
 - Totally erratic wide-complex tracing.



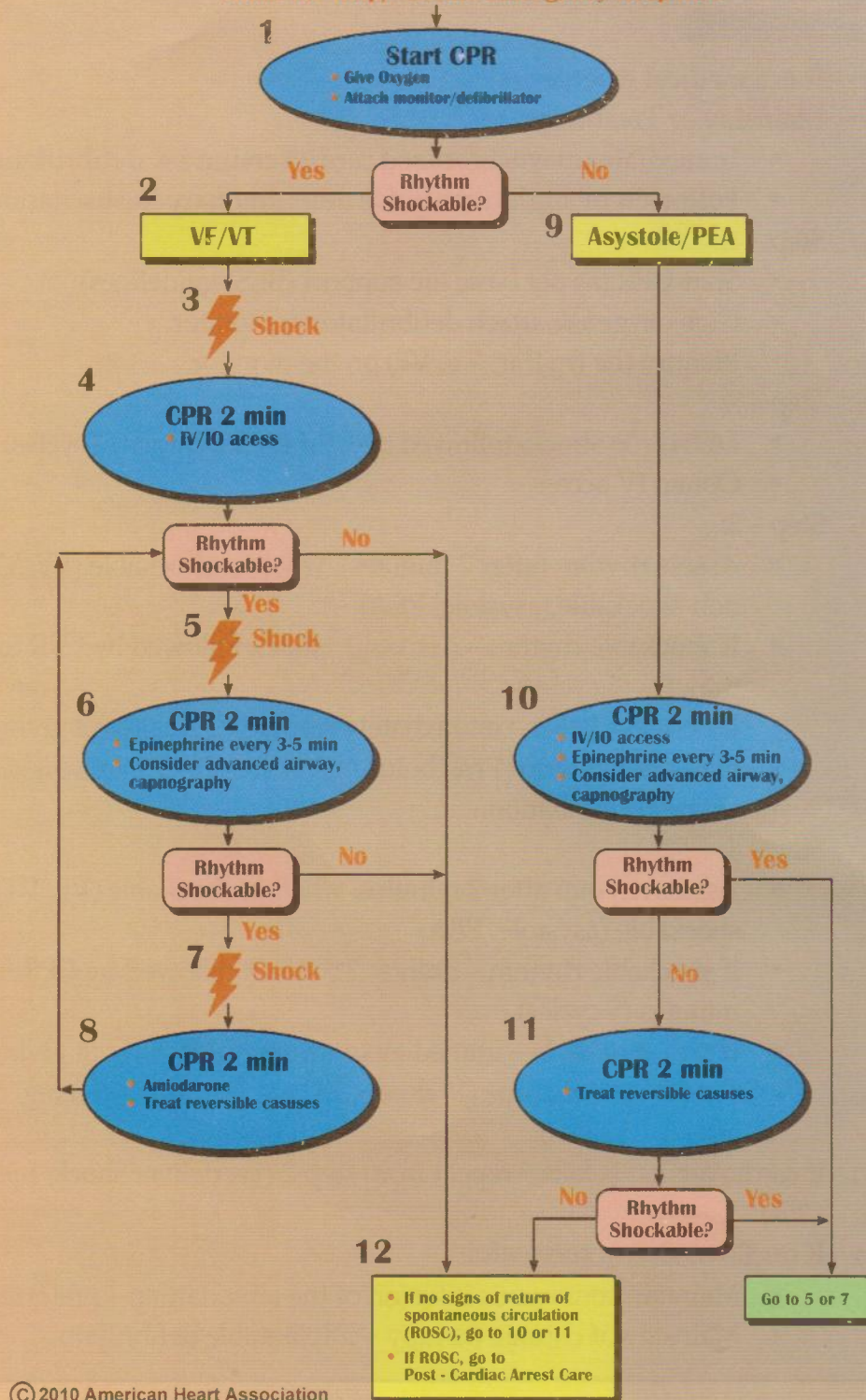
Ventricular Fibrillation

R_x**Treatment:**

- It is a medical emergency!
- Mainstay of Treatment:
 - Immediate unsynchronized cardioversion i.e. defibrillation
 - Followed by high-quality Cardiopulmonary Resuscitation (CPR).
- Step – 1:
 - Start CPR (as per basic life support (BLS) guidelines)
 - Give oxygen & attach defibrillator & monitor.
 - Identify the rhythm (i.e. VF) on the monitor.
- Step – 2:
 - **Deliver 1st Shock**, followed by CPR for 2 minutes (5 cycles)
 - Obtain IV access
- Step – 3:
 - Assess rhythm (after 2 minutes), whether shockable (VF, VT) or non-shockable (asystole, PEA)
 - If shockable rhythm – **deliver 2nd shock** followed by CPR for 2 minutes (5 cycles)
 - If non-shockable – immediately resume CPR without giving shock.
 - Start epinephrine (1 mg bolus, then every 3 – 5 minutes)
 - Consider intubation
- Step – 4:
 - Assess rhythm after 2 minutes, whether shockable (VF, VT) or non-shockable (asystole, PEA)
 - If shockable rhythm – **deliver 3rd shock** followed by CPR for 2 minutes (5 cycles)
 - If non-shockable – immediately resume CPR without giving shock.
 - Start IV amiodarone (1st dose = 300 mg, 2nd dose = 150 mg, given after 3 – 5 mins)
- If cardioversion fails = repeat from step-2 (i.e. deliver shock, followed by CPR)
- If cardioversion is successful:
 - Maintain continuous infusion of the amiodarone – preferred agent.
 - Mainstay of chronic therapy – implantable defibrillator

Adult Cardiac Arrest

Shout for Help/Activate Emergency Response



II. Ventricular Tachycardia (VT):

- It is defined as ≥ 3 consecutive premature ventricular contractions (PVCs), at a rate of between 100 and 250 bpm.
- Non-sustained VT is asymptomatic, while sustained VT (> 30 seconds) can lead to palpitations, hypotension, syncope, and pulselessness.
- **Causes:**
 - Coronary artery disease with prior MI – most common cause
 - Cardiomyopathies
 - Prolonged QT syndrome
 - Drug toxicity
- **ECG:**
 - **Wide and bizarre QRS complexes.**
 - In monomorphic VT, all QRS complexes are identical.
 - In polymorphic VT, the QRS complexes are different.



R_x

Treatment:

- Pulseless VT:
 - Exactly the same steps as for ventricular fibrillation (VF) – see above
 - Unsynchronized cardioversion + CPR
- Hemodynamically Unstable (with pulse):
 - Synchronized DC cardioversion – treatment of choice.
 - Follow with IV amiodarone to maintain sinus rhythm.
- Hemodynamically Stable:
 - Drugs – IV Amiodarone, IV Procainamide, or IV Sotalol.
 - If drugs fail, then synchronized cardioversion.



Clinical Pearl:

Monomorphic VT v/s SVT:

- It is difficult to distinguish monomorphic VT from SVT with aberrancy.
- Factors that favor VT over SVT are:
 - AV dissociation (pathognomonic)
 - History of MI
 - Very broad QRS complexes (> 140 msec)
 - No response to carotid sinus massage
 - No response to adenosine
 - Extreme left axis deviation

III. Torsades de Pointes:

- It is a rapid polymorphic ventricular tachycardia (VT).
- It is characterized by undulating rotations of QRS complexes around the ECG base line.
- It is a complication of prolonged ventricular repolarization (prolonged QT interval).
- Causes (increases QT-interval):
 - Congenital prolonged QT syndromes
 - Tricyclic antidepressants
 - Anti-cholinergics
 - Lithium
 - Quinidine
 - Procainamide
 - **Brugada Syndrome:**
 - It is a genetic disorder due to **defect in sodium channel function**.
 - It presents with polymorphic VT or sudden cardiac death.
 - ECG = RBBB & ST-elevation in V1 and V2, but not usually with prolonged QT.
 - Treatment = implantable defibrillator
- Treatment:
 - Treat the underlying cause.
 - Acute Treatment:
 - **IV magnesiumis given in all cases – acute treatment of choice**
 - Alternative agents: IV Isoproterenol.
 - Pacing:

- Atrial pacing will suppress the arrhythmia.
- Pacing increases heart rate, which, in turn, shortens QT interval (terminating torsades)
- Chronic Treatment:
 - **Beta-blockers (propranolol) – first line drug in congenital long QT syndrome.**
 - **Beta-blockers are contraindicated in “acquired” long QT syndrome**
(because bradycardia caused by these drugs can precipitate torsades)
 - Left stellate ganglion block
 - Implantable cardiac defibrillator



Torsades de Pointes

Non-Shockable Rhythm:

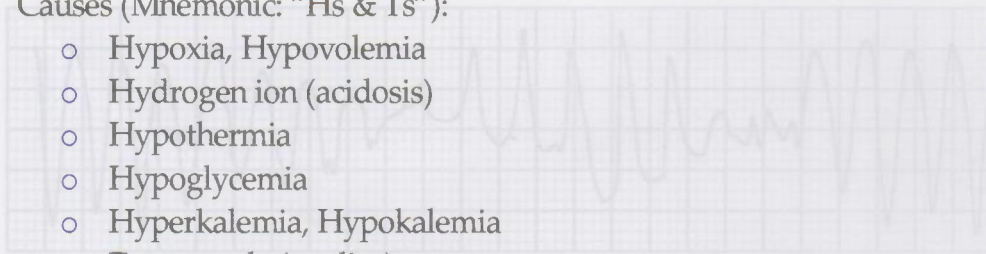
I. Asystole:

- It refers to loss of pulse as well as loss of electrical activity of heart.
- Management:
 - **Cardiopulmonary resuscitation (CPR) is the cornerstone for non-shockable rhythms.**
 - **Cardioversion is fruitless & detrimental** – eliminating any possibility of recovering a rhythm
 - Step – 1:
 - Cardiopulmonary resuscitation (CPR) for 2 minutes (5 cycles)
 - Give oxygen, attach monitor (defibrillator), and obtain IV access.
 - Step – 2:
 - Assess rhythm, whether shockable (VF, VT) or non-shockable (asystole, PEA)
 - If shockable – follow treatment steps of VF & VT (discussed above).
 - If non-shockable:
 - Start CPR for 2 minutes (5 cycles)

- Start epinephrine (1 mg bolus, then every 3 – 5 minutes)
- Consider intubation
- Treat reversible causes
- Step – 3:
 - Assess rhythm, whether shockable (VF, VT) or non-shockable (asystole, PEA)
 - If shockable – follow treatment steps of VF & VT (discussed above)
 - If non-shockable – repeat step-2 (i.e. CPR for 2 minutes)

II. Pulseless Electrical Activity (PEA):

- It refers to loss of pulse, in which electrical activity of heart is normal, but there is no motor contraction.
- Causes (Mnemonic: “Hs & Ts”):
 - Hypoxia, Hypovolemia
 - Hydrogen ion (acidosis)
 - Hypothermia
 - Hypoglycemia
 - Hyperkalemia, Hypokalemia
 - Tamponade (cardiac)
 - Tension pneumothorax
 - Thrombosis (Pulmonary Embolism)
 - Trauma
- Treatment:
 - It is same as for asystole (i.e. CPR)
 - Treat the underlying cause.



Coronary Heart Disease (CHD)

Introduction:

- Also known as "Ischemic Heart Disease" (IHD).
- It refers to an imbalance in coronary oxygen demand and supply resulting from insufficient blood flow.
- **Clinical Features:**
 - Asymptomatic
 - Stable angina
 - Acute coronary syndrome (ACS):
 - Unstable angina
 - Myocardial infarction (MI):
 - ST-elevation MI (STEMI)
 - Non-ST elevation MI (NSTEMI)
 - Sudden cardiac death
- **Risk Factors:**
 - Hypertension – most common risk factor
 - Diabetes mellitus – most dangerous (worst) risk factor
 - Cigarette smoking
 - Hyperlipidemia
 - Age (men > 45 years, women > 55 years)
 - Family history (CHD in first-degree relatives):
 - Male relative < 55 years old
 - Female relative < 65 years old
- **Chest Pain of Cardiac Origin:**
 - It is central and diffuse.
 - It is gradual in onset and takes several minutes to develop.
 - It is < 30 minutes in angina and > 30 minutes in MI.
 - It is dull, constricting, crushing, and choking in character.
 - It may radiate to the neck, jaw, and arm.
 - It occurs during (not after) exertion, but also occurs during emotion and in a cold wind.
 - It is relieved by rest and nitrates in angina, but not so in MI.
 - It is (especially MI) usually associated with breathlessness, sweating, nausea, and vomiting.
 - No changes with respiration or position of the body.

Differential Diagnosis of Chest Pain

<u>Tietze's syndrome</u>	<ul style="list-style-type: none"> It refers to costochondritis. It presents with chest wall tenderness.
<u>Aortic dissection</u>	<ul style="list-style-type: none"> Tearing chest pain radiating to back. Unequal blood pressure between arms.
<u>Pericarditis</u>	<ul style="list-style-type: none"> Chest pain that changes with position of the body. Chest pain aggravates with lying flat, improves when sitting up.
<u>Gastroesophageal reflux</u>	<ul style="list-style-type: none"> Chest pain is burning in nature. Bad taste, cough, and hoarseness.
<u>Pneumonia</u>	<ul style="list-style-type: none"> Cough sputum, hemoptysis and fever. Consolidation on CXR
<u>Pulmonary embolism</u>	<ul style="list-style-type: none"> Sudden onset shortness of breath Tachycardia, tachypnea, and hypoxia
<u>Pneumothorax</u>	<ul style="list-style-type: none"> Sharp, pleuritic pain (aggravated with inspiration) Tracheal deviation
<u>Peptic Ulcer Disease</u>	<ul style="list-style-type: none"> Epigastric discomfort. Duodenal ulcer relieved with food, gastric ulcer aggravated with food.

Stable Angina:

- It refers to substernal chest pain secondary to myocardial ischemia.
- Pathogenesis: ischemia due to **fixed atheromatous stenosis** of ≥ 1 coronary arteries.
- Clinical Features:**
 - Substernal chest pain of 5 – 15 minutes duration.
 - Relieved by rest or nitrates.
 - Aggravated by physical exertion, heavy meals, cold exposure, and intense emotion.
 - Pain may radiate to jaw, neck, and arm.
 - Pain may be associated with nausea, vomiting, sweating or lightheadedness.
- Investigations:**
 - Resting ECG:**
 - It is the best initial test.
 - Sign of myocardial ischemia i.e. ST-depression and T-wave inversion.
 - It is usually normal in patients with stable angina.

○ **Exercise ECG:**

- Also known as “exercise tolerance test” (ETT).
- It involves recording ECG before, during, and after exercise on a treadmill.
- **A patient with a positive stress test should undergo cardiac catheterization.**
- It is sensitive if the patient is able to increase heart rate to 85% of the maximum.

(Maximum Heart Rate = 220 – Age)

- Signs of myocardial ischemia to look for on ECG:
 - Planar ST depression = Ischemia
 - Down-sloping ST depression = Ischemia
 - Up-sloping ST depression = Normal (non-specific)
- Exercise ECG depends on two factors:
 - The patient is able to exercise
 - There are no baseline ECG abnormalities

(i). What If There Are Baseline ECG Abnormalities?

- Baseline ECG abnormalities interferes with detection (reading) of ischemia.
- In such patients two methods can be used to detect ischemia (without ECG):
 - Exercise thallium scan
 - Exercise echocardiography

(ii). What If the Patient Cannot Exercise?

- In such a scenario, two methods can be used to detect ischemia.
 - Pharmacologic (Dipyridamole) Thallium Scan
 - Pharmacologic (Dobutamine) Echocardiography

○ **Myocardial Perfusion Scanning (Thallium Scan):**

- It is done in patients with equivocal exercise tolerance test and those who are unable to exercise.
- It involves obtaining scintiscans of the myocardium at rest and during stress after the administration of IV radioactive isotope.
- Types of Stress:
 - Exercise
 - Pharmacologic (dipyridamole) – for those who can't exercise
- Interpretation:
 - Reversible ischemia = perfusion defect during stress, but not at rest
 - Irreversible ischemia (infarction) = perfusion defect during stress & at rest.

○ **Stress Echocardiography:**

- It is an alternative to myocardial perfusion scanning.
- It uses transthoracic echocardiography to identify myocardial ischemia & infarction
- Types of Stress:
 - Exercise echocardiography
 - Pharmacologic (dobutamine) echo – for those who can't exercise.
- Interpretation:
 - Reversible ischemia = decreased wall motion during stress
 - Irreversible ischemia (infarction) = decreased wall motion during stress & at rest

○ **Coronary Angiography (Arteriography):**

- It is used to detect the anatomic location of coronary artery disease.
- **It is the most accurate test of detecting coronary artery disease.**
- It provides information as to which procedure is preferable:
 - Coronary artery bypass graft (CABG) surgery, OR
 - Percutaneous coronary intervention (PCI)



Clinical Pearl:

Types of Stress Testing:

- Exercise tolerance test:
 - Ischemia is detected by ST segment depression.
- Exercise echocardiography = Dobutamine echocardiography:
 - Ischemia is detected by wall motion abnormalities.
- Exercise thallium = Dipyridamole thallium:
 - Ischemia is detected by perfusion defects.

R
X**Management:****(i). Lifestyle Modifications:**

- Smoking cessation
- Weight reduction
- Regular exercise
- Diet: reduce intake of saturated fat and cholesterol (<200mg/day)
- Control blood pressure
- Treat hyperlipidemia:
 - Decreased cholesterol intake.
 - Statins i.e. HMG-CoA reductase inhibitors (e.g. simvastatin)

(ii). Anti-platelet Therapy:

- Aspirin:
 - It is indicated in all patients with CAD.
 - It should be given as low-dose (75 mg daily) indefinitely.
- Clopidogrel:
 - It is equally effective as aspirin, given as 75mg daily.
 - It is given for those who cannot tolerate aspirin.

(iii). Anti-anginal Therapy:

1. Nitrates
 2. Beta blockers
 3. Calcium channel blockers
 4. Potassium channel activators
 5. If Channel antagonists
- **Nitrates:**
 - These agents (e.g. glyceryl trinitrate GTN) cause venous and arteriolar dilatation.
 - These agents decrease both preload and afterload.
 - GTN can be given orally, sublingually, transdermal or intravenously.
 - GTN undergoes extensive first-pass metabolism in liver, and is ineffective orally.
 - Side effects:
 - Headache
 - Orthostatic hypotension

○ **Beta Blockers:**

- These agents block sympathetic stimulation and lower myocardial O₂ demand.
- Cardio-selective β -blockers (metoprolol) are better tolerated than non-selective β -blockers (propranolol).
- Side effects:
 - Bronchospasm (non-selective β -blockers)
 - **Withdrawal syndrome:** abrupt withdrawal of β -blockers may have a rebound effect and precipitate dangerous arrhythmias or MI.

○ **Calcium Channel Blockers (CCBs):**

- These agents cause coronary vasodilation and afterload reduction.
- Dihydropyridine CCB:
 - These are nifedipine and nicardipine
 - These agents cause reflex tachycardia & therefore must be given with β -blockers.
- Non-Dihydropyridine CCB:
 - These are verapamil and diltiazem.
 - These agents must not be given with β -blockers as it may result in profound bradycardia.
 - It is therefore suitable in those who cannot tolerate β -blockers (e.g. asthmatics)
- Side effects:
 - Myocardial depression; Heart failure
 - Constipation
 - Peripheral edema
 - Flushing, headache, dizziness

○ **Potassium Channel Activators:**

- Like nitrates these agents cause venous & arteriolar dilatation.
- Unlike nitrates these agents are not associated with pharmacologic tolerance.
- **"Nicorandil"** is the only drug in this class.
- It is given as 10 – 30 mg twice daily orally.

○ **If Channel Antagonist:**

- **"Ivabradine"** is the first of this class of drug.
- It acts on the If inward current in the SA node, reducing the heart rate.

(iv). Revascularization Therapy:○ **Percutaneous Coronary Angiography (PCI):**

- It is commonly referred to as "angioplasty".
- It consists of both coronary angioplasty with a balloon and stenting.
- Indications:
 - Acute coronary syndrome with ST-segment elevation
 - Should be considered in single or two-vessel disease.
 - Should also be considered even in three-vessel disease
 - Stable angina – provides symptomatic relief, but it is UNCLEAR if it improves survival in chronic stable angina
- Complications:
 - Acute = occlusion of the target vessel:
 - It occurs in 2 – 5% of procedures.
 - It is due occlusion of vessel by a thrombus or coronary artery dissection.
 - Chronic = re-stenosis of the dilated vessel:
 - It tends to occur within 3 months of procedure.
 - It is due to a combination elastic recoil & smooth muscle proliferation.

○ **Coronary Artery Bypass Grafting (CABG):**

- It is a surgical method of revascularization.
- It involves bypassing the stenotic coronary vessels using grafts.
- Grafts can arterial (internal mammary artery, radial artery) or venous (saphenous vein).
- Arterial grafts have long-term patency than venous grafts. ($\approx 50\%$ of vein grafts are patent 10 years after surgery, while $\approx 80\%$ arterial grafts are patent at 10 years.)
- **Indications (Improves Survival):**
 - Three-vessel disease with at least 70% stenosis in each vessel. (Left anterior descending (LAD), circumflex, & right coronary arteries).
 - Left main coronary disease
 - Two-vessel disease in a patient with diabetes
- Complications:
 - Peri-operative Stroke (1 – 5%)
 - Short-term cognitive impairment (resolves within 6 months)
 - Long-term cognitive decline (more than 30% of patients at 5 years)

	<u>PCI</u>	<u>CABG</u>
Mortality	Less (<0.5%)	More (<1.5%)
Myocardial infarction	2%	10%
Hospital stay	12 – 36 hours	5 – 8 days
Return to Work	2 – 5 days	6 – 12 weeks
Neurologic complications	Rare	Common
Recurrent angina	More common 15 – 20% at 6 mo	Less common 10% at 1 year



Clinical Pearl:

Angina with Normal Coronary Arteries:

Variant Angina:

- Also known as “**Prinzmetal’s angina**”.
- It involves transient coronary vasospasm.
- It is usually accompanied by a fixed atheromatous lesion, but can occur in normal coronary arteries.
- Patient is usually young female; history of smoking
- ECG = **transient ST-elevation** (not depression).
- Treatment = calcium channel blockers and nitrates.

Syndrome X:

- It refers to:
 1. Typical angina on exertion
 2. Evidence of myocardial ischemia on stress testing.
 3. Angiographically normal coronary arteries

Acute Coronary Syndrome (ACS):

I. Introduction:

- ACS is a term used to describe:
 - Unstable angina
 - Non-ST elevation MI (NSTEMI)
 - ST elevation MI (STEMI)
- ACS is due to rupture of coronary atheromatous plaque with superimposed thrombus formation.
- All these components are part of ACS, because their initial presentation & early management are similar.

■ Definitions:

- Unstable Angina (UA): *crescendo*
 - It is defined as new-onset angina or rapidly worsening angina (crescendo angina) or angina occurring at rest.
 - It is not associated with myocardial damage (negative cardiac enzymes).
 - ECG shows ST-depression \pm T-wave inversion.
- NSTEMI:
 - It is defined as localized area of myocardial necrosis (elevated cardiac enzymes) without ST-elevation.
 - ECG shows ST-depression \pm T-wave inversion.
- STEMI:
 - It is defined as localized area of myocardial necrosis (elevated cardiac enzymes).
 - ECG shows ANY ONE of the following:
 - ST-segment elevation of ≥ 1 mm in two contiguous limb leads.
 - ST-segment elevation of ≥ 2 mm in two contiguous chest leads.
 - New left bundle branch block (LBBB)

Spectrum of Acute Coronary Syndrome			
Diagnosis	Unstable Angina	NSTEMI	STEMI
Coronary thrombosis	Sub-total		Total
History	Angina that is new-onset, OR Angina occurring at rest; < 30 minutes		Angina occurring at rest > 30 minutes
ECG	ST depression; T-wave inversion		ST-elevation
Cardiac enzymes	Negative	Positive	Positive

II. Clinical Features:

- Chest pain is the cardinal symptom; it is retrosternal radiating to jaw, neck, and arms.
- Chest pain may be associated with breathlessness, vomiting, and collapse.
- Chest pain is more severe and lasts longer than angina.
- Chest pain is often described as a tightness, heaviness, and constriction in the chest.
- Signs:
 - Signs of heart failure = raised JVP, crackles in lung fields, S3 heart sound,
 - Signs of ischemia = S4 heart sound, new mitral regurgitation murmur.
- **Most common cause of death:**
 - Within the 1st hour = arrhythmia (VF or VT)
 - After 1st few hours = heart failure
- Killip Class:
 - It refers to categorization of the severity of heart failure.
 - Class I = no heart failure (6% mortality)
 - Class II = crackles audible halfway up the chest OR S3 (17% mortality)
 - Class III = crackles audible in all the lung fields (30 – 40% mortality)
 - Class IV = cardiogenic shock. (60 – 80% mortality)

III. Investigations:

- **ECG:**
 - It is the best initial test and central to confirming the diagnosis.
 - A single normal ECG does NOT exclude ACS – therefore, serial ECG should be obtained.
 - ECG changes:
 - “Peaked T-waves”= occur very early & may be missed

- **"ST-segment deviation"** = earliest change that is most commonly detected.
 - ST-segment elevation = indicates transmural injury
 - ST-segment depression = indicates subendocardial injury
- **"Q-waves"** = indicates prior infarction
- **"T-wave inversion"**

<u>Area of Infarction</u>	<u>Leads</u>	<u>Artery Involved</u>
Inferior wall MI	II, III, aVF	Right coronary artery
Anterior wall MI	V3 and V4	Left anterior descending (LAD)
Anteroseptal MI	V1, V2, V3, V4	Left anterior descending (LAD)
Anterolateral wall MI	V4 – V6, I, and aVL	Left anterior descending or circumflex
Posterior wall MI	Tall R waves & ST-depression in V1–V4, tall upright T-wave.	Posterior descending

- **Cardiac Enzymes:**
 - Unstable angina doesn't cause a rise in cardiac enzymes.
 - MI (both STEMI and NSTEMI) causes a rise in plasma levels of cardiac enzymes.
 - Creatinine Kinase (CK-MB):
 - **It is the first cardiac enzyme to rise and fall.**
 - **It is the enzyme of choice to check for re-infarction within a few days of first cardiac event.**
 - Starts to rise = 4 – 6 hours
 - Peak = 12 hours
 - Back to normal = 48 – 72 hours
 - Troponins (T and I):
 - **It is the most sensitive cardiac enzyme.**
 - It cannot distinguish re-infarction occurring several days after the first event.
 - Starts to rise = 4 – 6 hours
 - Back to normal = 2 weeks

IV.

R_x

Management (First 12 Hours):

(i). Analgesia:

- Adequate analgesia is essential for:
 - Reliving pain & distress
 - Decreasing adrenergic (sympathetic) drive, which, in turn reduces:
 - Vascular resistance, BP, and infarct size
 - Susceptibility to ventricular arrhythmias
 - Agents:
 - Intravenous opiates (IV morphine sulphate 5 – 10 mg) plus:
 - Anti-emetic (IV metoclopramide 10 mg)
 - Avoid intramuscular route (clinical effect is delayed due to poor skeletal muscle perfusion)

(ii). Anti-Thrombotic Therapy:

▪ Anti-Platelet Therapy:

Aspirin:

- Aspirin (300 mg) single oral dose (within 12 hours).
- Followed by aspirin (75mg) indefinitely.

P2Y₁₂ (ADP) Receptor Blockers:

- Clopidogrel:
 - 600 mg single dose (within 12 hours), followed by 150 mg daily for 1 week and 75 mg daily thereafter.
 - Clopidogrel + Aspirin is BETTER than aspirin alone in reducing the risk of death, MI and stroke.
- Ticagrelor:
 - 180 mg x once, followed by 90 mg twice daily.
 - It is more rapid (~30 min), more potent than clopidogrel.
 - It is more effective than clopidogrel in reducing vascular death, MI, and stroke.
 - There is NO overall major bleeding risk compared with clopidogrel.
 - Side-effects = dyspnea (most common), bleeding, rash, itching.
- Prasugrel:
 - It is mainly indicated in patients undergoing PCI for ACS.
 - 60 mg x once at PCI, then 10 mg QD (once daily).
 - Side-effects = bleeding risk
 - Avoid in patients > 75 years (risk of hemorrhagic stroke)

Glycoprotein IIb/IIIa Inhibitors (GPI):

- These agents are abciximab, eptifibatide, and tirofiban.
- These agents inhibit platelet aggregation & thrombus formation.
- These agents decrease death & MI when added to aspirin + clopidogrel in patients undergoing PCI.
- They are given as "infusion", 2 – 24 hours post-PCI.
- There is NO CLEAR BENEFIT for starting these agents prior to PCI.

▪ Anti-Coagulation Therapy:

- It reduces the risk of thromboembolic complications (stroke)
- It also reduces the progression of thrombus, and re-infarction, but does not lower mortality.
- It should be continued for 8 days or until discharge, or coronary revascularization.
- It is achieved using either of:
 - Unfractionated Heparin:
 - Monitor with aPTT (should be 1.5 – 2 x control)
 - Dosage: 60 U/kg IV bolus, then 12 U/kg/hour for 48 hours (or until end of PCI).
 - Enoxaparin:
 - It is low-molecular weight heparin (LMWH).
 - Dosage: 1 mg/kg twice daily x SC (subcutaneous) (for 2 – 8 days).
 - Fondaparinux:
 - **It is factor Xa inhibitor, with the best safety and efficacy profile.**
 - Dosage: 2.5 mg QD (once daily) x SC (for 2 – 8 days)
 - Bivalirudin:
 - It is direct thrombin inhibitor.
 - Dosage: 0.75 mg/kg IV bolus at the time of PCI, then 1.75 mg/kg/hour.

(iii). Anti-Anginal Therapy:**▪ Nitrates:**

- Nitrates decrease mortality.
 - Dilate coronary arteries (increase blood supply)
 - Venodilation (decreases preload, and thus demand)
- Dosage:
 - Sublingual glyceryl trinitrate (300 – 500 µg) as first-aid in suspected ACS.

- Intravenous glyceryl trinitrate (0.6 – 1.2 mg/hour)
- Contraindications:
 - Hypovolemia
 - Symptomatic RV infarction
- **Beta-Blockers:**
 - Beta-blockers have been shown to decrease the mortality.
 - Beta-blockers should therefore, be part of long-term maintenance therapy.
 - Mechanism & benefits already discussed above.
 - Contraindications:
 - Moderate-to-severe heart failure (pulmonary edema)
 - Bradycardia (heart rate < 65 bpm)
 - Hypotension (systolic BP < 105 mmHg)
 - Severe bronchospasm

(iv). Reperfusion Therapy:

- Reperfusion Therapy involves using either:
 - Percutaneous Coronary Intervention (PCI), OR
 - Thrombolysis (fibrinolysis)
- Role of Reperfusion Therapy in UA & NSTEMI:
 - Reperfusion therapy is of NO USE, and can even be harmful:
 - PCI is not effective because the infarct-related artery is not occluded in 60–85% cases.
 - Thrombolysis is not effective because the non-occluding thrombi are “platelet-rich”.
- Role of Reperfusion Therapy in STEMI:
 - Reperfusion therapy is of prime importance in restoring the coronary artery patency:
 - PCI is effective because the infarct-related artery is occluded.
 - Thrombolysis is effective because the occluding thrombi are “fibrin-rich”.

(i). Primary Percutaneous Coronary Intervention (PCI):

- It is the treatment of choice for ST-elevation MI.
- It is more effective than thrombolysis, because it is associated with greater reduction:
 - Risk of death
 - Risk of recurrent MI; Stroke

- It should be performed within 90 minutes of first medical contact of patient with MI.
- It gives better results when combined with glycoprotein IIb/IIIa receptor inhibitors.
- When primary PCI cannot be achieved within 2 hours of diagnosis, thrombolysis should be performed.

(ii). Thrombolysis:

- It is performed in non-PCI capable hospital.
- It can be administered within the 12 hours of hospital presentation.
- **However, the benefit is greatest within 2 hours (ideally 30 minutes).**
- Most common complication = bleeding (intracerebral hemorrhage)
- It can be performed using:
 - Alteplase:
 - It is tissue plasminogen activator (tPA) – agent of choice
 - Dosage: 15 mg IV bolus, then 0.75 mg/kg over next 30 minutes, then 0.5 mg/kg over the next 60 minutes (given over 90 minutes).
 - Streptokinase:
 - Alteplase is associated with better survival rates compared to streptokinase
 - Alteplase is associated with higher risk of intracerebral bleeding than streptokinase.
- Indications for Thrombolysis:
 - STEMI less than 12 hours (best within first 2 hours)
 - ECG shows ANY ONE of following:
 - ST-segment elevation of ≥ 1 mm in two contiguous limb leads.
 - ST-segment elevation of ≥ 2 mm in two contiguous chest leads.
 - New left bundle branch block (LBBB)
 - Thrombolysis is harmful if given to:
 - Patients who present > 12 hours after the onset of symptoms.
 - Patients with normal ECG or ST-depression.
- Absolute Contraindications for Thrombolysis:
 - Hemorrhagic stroke
 - Ischemic stroke in preceding 3 months
 - CNS neoplasm
 - Active internal bleeding or known bleeding diathesis
 - Aortic dissection

- Relative Contraindications for Thrombolysis:
 - Transient ischemic attack (TIA) in preceding 6 months
 - Major surgery in preceding 3 weeks
 - Major head trauma in preceding 3 weeks
 - Uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg)
 - Current use of oral anticoagulants
 - High probability of active peptic ulcer
 - Pregnancy



Clinical Pearl:

- "Door to Balloon Time" i.e. PCI is under 90 minutes.
- "Door to Needle Time" i.e. thrombolysis is under 30 minutes.
- Thrombolysis is beneficial only with STEMI.
- Heparin is best for NSTEMI.
- GP IIb/IIIa inhibitors are best for NSTEMI and those undergoing PCI & stenting.

V. Long-Term Post-ACS Management:

- Life style modifications (already discussed).
- Medications:
 - Aspirin & Clopidogrel:
 - **Dual anti-platelet (aspirin + clopidogrel) should be given for at least 3 months.**
 - Dual anti-platelet therapy & PCI:
 - At least for 30 days in patients who receive a bare-metal stent.
 - At least for 12 months in patients who receive a drug-eluting stent.
 - Beta-blockers
 - Nitrates
 - Statins:
 - Serum cholesterol should be measured within 24 hours of presentation.
 - This is because serum cholesterol falls transiently in the first 3 months post-MI.

- Irrespective of serum cholesterol concentration, all patients should receive statin therapy post-ACS.
- Stating therapy e.g. Atorvastatin 80 mg daily.
 - Target LDL < 100 mg/dL.
 - Target HDL > 40 mg/dL.
 - Target triglycerides < 150 mg/dL.
- ACE-Inhibitors:
 - Initiate within hours of hospitalization if there are no contraindications.
 - Best mortality benefit is seen in patients with acute MI and LV systolic dysfunction (EF < 35%).
 - It should be part of maintenance therapy due to following advantages:
 - Improves survival
 - Counteract ventricular remodeling
 - Prevent the onset of heart failure
 - Reduce risk of recurrent MI
- Implantable Cardiac Defibrillator (ICD):
 - It is helpful in prevent sudden cardiac death in patients with acute MI and LV systolic dysfunction (EF ≤ 30%)

VI. Complications of MI:

(i). Arrhythmia:

- It is the major cause of death in those who die before receiving medical attention.
- It is seen in 5 – 10% of cases.
- It may be due to:
 - Ventricular fibrillation
 - Ventricular tachycardia

(ii). Bradycardia:

- Sinus Bradycardia:
 - Observation only = if asymptomatic
 - IV atropine = if symptomatic (hemodynamic deterioration)
- AV Blocks:
 - 1st & 2nd-degree (Mobitz-type-I) AV blocks = do not require treatment
 - 2nd-degree (Mobitz-type-II) & 3rd-degree AV Blocks:
 - Anterior MI:
 - Requires prophylactic temporary pacemaker

- Because the risk of asystole is high.
- Inferior MI:
 - It is temporary (resolves with reperfusion therapy)
 - If symptomatic – consider temporary pacemaker.

(iii). Right Ventricular Infarction:

- It is mostly seen with inferior wall myocardial infarction.
- It presents with tachycardia, hypotension and clear lungs.
- Diagnosis:
 - Flip the ECG leads from the usual left side of chest to the RIGHT side.
 - **ST elevation in right V4** is the most specific finding.
- Treatment:
 - High-volume fluid replacement
 - Avoid nitroglycerin (they worsen cardiac filling)

(iv). Ventricular Free Wall Rupture:

- It is the most common mechanical complication following MI.
- It presents as **cardiac tamponade and is usually fatal**.
- It occurs most frequently at day 3 – 7 after the onset.
- Treatment = pericardiocentesis, inotropes, and surgery

(v). Rupture of Papillary Muscles:

- It is a mechanical complication presenting with acute mitral regurgitation.
- It presents with **pansystolic murmur, S3, acute pulmonary edema and shock**.
- Diagnosis: echocardiography
- Treatment: emergency mitral valve replacement

(vi). Inter-ventricular Septal Rupture:

- It is a mechanical complication that results in an acquired (VSD).
- It is therefore a **“left-to-right shunt”** presenting with pansystolic murmur radiating to the right sternal border.
- It is characterized by **“oxygen step-up”** from right atrium to right ventricle (because oxygenated blood from LV enters RV, increasing oxygen saturation).
- In this condition patients present with **“right-heart failure”**, unlike rupture of papillary muscle (acute MR), which presents with pulmonary edema.
- Treatment = surgery

(vii). Pericarditis:

- It refers to inflammation of pericardium and occurs on **2nd – 3rd day post-MI**.
- Clinical Features:

- Chest pain, which is pleuritic & positional
- It aggravates on deep inspiration & lying down.
- It is relieved by sitting up and leaning forward.
- It has positive pericardial rub.
- Treatment:
 - High dose aspirin, & opioids
 - **NSAIDs & steroids contraindicated** – (risk of ventricular aneurysm & myocardial rupture)
 - **Dressler's Syndrome:**
 - Also known as “post-myocardial infarction syndrome”.
 - It is pericarditis of autoimmune origin.
 - It occurs **2 – 10 weeks post MI**.
 - It presents with pericarditis, pleuritis, fever, malaise, and leukocytosis.
 - Treatment:
 - High-dose aspirin – first-line agents
 - NSAIDs & steroids (alternative options)



Summary:

Emergency Management of ACS: mnemonic MONA- therapy

1. Morphine
2. Oxygen – nasal cannula 2 – 4 L/min.
3. Nitrates – sublingual GTN
4. Aspirin & Clopidogrel
5. Investigations (CBC, biochemistry, glucose)
6. 12 – lead ECG
7. Beta blockers (if no contraindication)
8. If primary PCI available then give Gp IIb/IIIa inhibitors
9. Alternatively give thrombolysis

Congestive Heart Failure (CHF)

I. Introduction:

- It is a condition in which the heart is unable to pump blood at a rate required to meet the metabolic demand of the body's tissues and organs.
- **Mechanism:**
 - Decreased cardiac output results in neuro-humoral activation:
 - Sympathetic Nervous System Activation:
 - This results in vasoconstriction and increased afterload.
 - This, in turn, increases BP and cardiac work.
 - Renin-Angiotensin-Aldosterone System Activation:
 - This results in Na & H₂O retention, which increase intravascular volume
 - This, in turn, increases BP and cardiac work.

▪ **Types of Heart Failure:**

(i). Systolic Dysfunction:

- It is due to impaired contractility.
- It therefore has LOW EJECTION FRACTION.
 - Ischemic heart disease, especially MI – most common cause
 - Hypertension (resulting in cardiomyopathy)
 - Valvular Heart Disease
 - Dilated cardiomyopathy
 - Myocarditis
 - Hemochromatosis
 - Alcohol
 - Thyroid disease

(ii). Diastolic Dysfunction:

- It is due to impaired ventricular filling during diastole.
- It therefore has NORMAL EJECTION FRACTION.
 - Hypertension leading to myocardial (left ventricular) hypertrophy
 - Valvular Heart Diseases
 - Hypertrophic cardiomyopathy
 - Restrictive cardiomyopathy (amyloidosis, sarcoidosis, hemochromatosis)
 - Constrictive pericarditis
 - Cardiac tamponade

II. Clinical Features:

(i). Left-sided Heart Failure:

- It is the most common type of heart failure.
- It is a "forward failure" because the left-side of heart cannot eject blood into aorta.
- This decreased left ventricular output results in increased left atrial pressure & pulmonary venous pressure, which causes:
 - Pulmonary congestion
 - Pulmonary edema
- Clinical Features:
 - Symptoms:
 - Dyspnea (difficulty breathing)
 - Orthopnea:
 - Dyspnea on lying flat, relieved by elevation of the head with pillows.
 - Lying flat increases venous return to the heart, resulting in pulmonary congestion.
 - Paroxysmal nocturnal dyspnea (PND):
 - It refers to sudden attacks of extreme dyspnea occurring at night.
 - It wakes the patient from sleep, associated with anxiety, & suffocation.
 - It has same mechanism as for orthopnea.
 - It gets relieved after sitting up.
 - Signs:
 - **S3 heart sound – (first cardiac sign)**
 - Bibasilar inspiratory crackles on chest auscultation.
 - Functional mitral valve regurgitation – (pansystolic murmur).
 - Cardiac asthma:
 - It refers to expiratory wheezes in patients with heart failure.
 - It is due to peri-bronchiolar edema.

Clinical Pearl:

Left-Sided Heart Failure & Pulmonary Edema:

- ACUTE increase in left atrial (LA) pressure results in pulmonary edema.
- GRADUAL increase in LA pressure leads to reflex pulmonary vasoconstriction, which protects the patient from pulmonary edema.
- This gradual increase in LA pressure explains absence of pulmonary edema in MS.

(ii). Right-sided Heart Failure:

- It is a “backward failure” because the right side of the heart cannot pump blood from venous system to the lungs and blood accumulates in the venous system.
- Causes:
 - Left-sided heart failure – most common cause
 - Chronic lung disease (cor pulmonale)
 - Pulmonary valvular stenosis
 - Pulmonary embolism
- Clinical findings:
 - Jugular venous distention (JVD)
 - Right-sided S₃ and S₄ heart sound
 - Functional tricuspid valve regurgitation
 - Painful hepatomegaly
 - Ascites
 - Edema:
 - Pitting pedal and pretibial edema (a hallmark of right-sided HF)
 - Generalized edema (anasarca)

Framingham Diagnostic Criteria for Heart Failure

Diagnosis Requires Concurrent Presence of 2 Major Criteria, OR, 1 Major & 2 Minor Criteria

<u>Major Criteria</u>	<u>Minor Criteria</u>
Paroxysmal Nocturnal Dyspnea (PND)	Nocturnal cough
Weight loss of 4.5 kg in 5 days in response to treatment	Dyspnea on exertion
Jugular Venous Distention (JVD)	A decrease in vital capacity by 1/3 rd the maximal value recorded
Hepatojugular Reflux	Pleural effusion
S3 heart sound	Tachycardia (120 bpm)
Rales	Hepatomegaly
Central Venous Pressure (CVP) > 16 cm of water	Bilateral ankle edema
Circulation time of 25 second	
Radiographic cardiomegaly	
Autopsy findings of pulmonary edema, visceral congestion, or cardiomegaly	
Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. <i>J Am Coll Cardiol.</i> 1993 Oct; 22(4 suppl A):6A-13A	

(iii). High-output Heart Failure:

- It refers to congestive heart failure with high cardiac output.
- Causes:
 - Severe anemia
 - Wet beriberi (thiamine deficiency i.e. vitamin B1)
 - Arteriovenous fistula
 - Paget's disease of bone
 - Hyperthyroidism
 - Pregnancy
 - Mitral regurgitation, Aortic regurgitation

New York Heart Association (NYHA) Classification

Class I	No limitation during ordinary activity
Class II	Slight limitation during ordinary activity
Class III	Marked limitation of normal activities without symptoms at rest.
Class IV	Dyspnea at rest; all activities cause dyspnea.

American College of Cardiology (American Heart Association) Heart Failure Staging

Stage A	No structural heart disease or symptoms of heart failure
Stage B	Structural heart disease but no symptoms of heart failure
Stage C	Structural heart disease and symptoms of heart failure
Stage D	Refractory heart failure requiring specialized interventions

**Clinical Pearl:****Dyspnea of Cardiac Origin:**

- Dyspnea on exertion is the most common symptom of congestive heart failure.
- The features that differentiate cardiac dyspnea from dyspnea of other origins are:
 1. Orthopnea
 2. Paroxysmal nocturnal dyspnea (PND)
 3. S3 heart sound

III. Investigations of CHF:

- Blood Tests:
 - CBC (anemia), UCE (electrolyte abnormalities, renal failure)
 - LFTs (impaired liver function), TFTs (hypothyroidism, hyperthyroidism)
 - Cardiac enzymes (acute heart failure), Brain natriuretic peptide (BNP).
- Chest X-ray:
 - Cardiomegaly
 - Pulmonary edema
- ECG:
 - Ischemia; left ventricular hypertrophy (LVH), previous MI,
 - Heart block, Arrhythmias
- Echocardiography:
 - **It is the most important of all tests of CHF.**
 - It distinguishes systolic dysfunction from diastolic dysfunction.
 - Determination of Ejection Fraction:
 - **Best Initial Test = Transthoracic Echocardiography (TTE)**
 - Most accurate test:
 - Nuclear ventriculography
 - Multiple-gated acquisition scan (MUGA)
 - Trans-Esophageal Echocardiography (TEE):
 - It is highly accurate for evaluating heart valve function & diameter.
 - It is, however, NOT necessary for evaluating CHF.

Clinical Pearl:

Brain Natriuretic Peptide (BNP):

- BNP is a cardiac neuro-hormone produced by ventricular myocardium.
- BNP helps distinguish CHF from other causes of dyspnea such as pulmonary embolus, asthma, and pneumonia.
- BNP is increased in CHF. **If BNP level is normal it excludes CHF.**
- BNP is elevated in conditions associated with left ventricular systolic dysfunction.
- **The higher the BNP, the higher the cardiovascular and all-cause mortality.**

IV.**R_x****Management:**▪ **Lifestyle Modifications:**

- Smoking cessation
- Weight reduction
- Low-sodium diet (< 4g/day)
- Exercise

▪ **Management of Systolic Dysfunction:**

- Following modalities lower mortality in CHF and are therefore the cornerstone of management of CHF with systolic dysfunction.

Modalities that Lower Mortality in Systolic Dysfunction:

1. ACE inhibitors & Angiotensin Receptor Blockers (ARBs)
2. Beta blockers
3. Spironolactone
4. Hydralazine + Nitrates
5. Implantable defibrillator

ACE (angiotensin-converting enzyme) Inhibitors:

- These agents include captopril, enalapril, and lisinopril.
- These should be given to all patients with systolic dysfunction at any stage of disease.
- Mechanism:
 - Prevents conversion of angiotensin I to angiotensin II (potent vasoconstrictor)
 - Cause venous & arterial dilation, decreasing preload & afterload.
- Side Effects:
 - Dry cough – most common
 - Hypotension
 - Renal failure
 - Hyperkalemia
 - Angioedema (Enalapril)



Clinical Pearl:

ACE-Inhibitors & Diuretics:

- ACE-Inhibitor + Diuretic should be the **initial** treatment in most symptomatic patients.
- If the patient is stable (SBP > 100 mmHg), ACE-I can be started in combination with diuretic.
- If the patient is unstable (SBP < 100 mmHg):
 - Withhold diuretics for 24 hours.
 - Then start a long-acting ACE-inhibitor at a small dose, preferably at night.
 - Starting at a low dose prevents symptomatic hypotension.

ARBs (aldosterone receptor blockers):

- These agents include losartan, candesartan, and valsartan.
- These can be used in patients who cannot tolerate ACE-inhibitors (e.g. dry cough)
- These agents are better tolerated with similar efficacy as compared to ACE-inhibitors.
- Mechanism:
 - These drugs block angiotensin receptors.
 - This prevents action of angiotensin-II on the heart, peripheral vasculature, & kidneys.
- Side-Effects:
 - Renal failure
 - Hyperkalemia

Beta Blockers:

- These agents are an integral part of CHF therapy.
- Not all beta-blockers are equal, the preferred agents are therefore, metoprolol, bisoprolol, and carvedilol.
- These agents are more effective than ACE-I at reducing mortality.
- Dosage:
 - **Always start at small incremental doses.**
 - **Starting at standard dose may precipitate acute-on-chronic heart failure.**

Diuretics:

- These agents decrease preload by increasing urinary Na & water excretion.

- These agents are used for **SYMPTOMATIC RELIEF** (due to volume overload)
- They **do not lower mortality**.
- These agents cause hypokalemia.
- Agents:
 - Loop diuretics (furosemide) – highly potent
 - Thiazide diuretics (hydrochlorothiazide) – modestly potent

Potassium-Sparing Diuretics:

- These agents are aldosterone receptor antagonist.
- Therefore, they cause urinary excretion of Na & water, and reabsorption of potassium.
- **Spironolactone lowers mortality, especially in advanced CHF (NYHA classes III & IV)**
- Eplerenone is an alternative to spironolactone.
- Complications:
 - Hyperkalemia
 - Gynecomastia (not seen with eplerenone)

Hydralazine + Nitrates:

- Nitrates are venodilators, therefore, they decrease preload.
- Hydralazine is arterial dilator, therefore, it decreases afterload.
- This combination causes vasodilation and reduces mortality.
- This combination indicated in those who cannot tolerate ACEI or ARBs (e.g. renal failure)

Ivabradine:

- It acts on the I_f inward current in the SA node.
- It therefore, reduces the heart rate (decreases oxygen demand).
- It reduces mortality in heart failure with moderate-to-severe systolic dysfunction.
- It is more effective in patients with relatively higher heart rate (> 77 bpm)
- It is ineffective in patients with atrial fibrillation.

Digoxin:

- It is a positive inotropic agent (increases contractility)
- It can be used for rate control in patients with CHF and atrial fibrillation.
- It decreases the likelihood of hospitalization for heart failure.
- It doesn't lower mortality.

▪ **Non-pharmacologic Treatment:**

Cardiac Resynchronization Therapy (CRT):

- It involves the use of biventricular pacemaker.
- It is indicated in symptomatic patients with ejection fraction of $\leq 35\%$ and QRS duration of $\geq 120\text{ms}$.
- It reduces mortality.

Implantable Cardiac Defibrillator (ICD):

- It lowers mortality by helping prevent sudden cardiac death.
- Indications:
 - Ejection fraction of $\leq 35\%$.
 - Class II-III symptoms despite optimal medical treatment.
 - For patients after 40 days post-MI (to prevent sudden cardiac death)

Ventricular Assist Devices (VADs):

- These devices assist cardiac output by helping the ventricles unload the blood.
- Indications:
 - As a bridge to cardiac transplantation
 - As a potential long-term therapy

Cardiac Transplantation:

- It is indicated in patients with intractable heart failure.
- Most common indications are coronary artery disease & dilated cardiomyopathy.
- Complications:
 - Infections
 - Accelerated atherosclerosis
 - Rejection:
 - Treated with high-dose steroids.
 - However, cardiac biopsy is often used to confirm the diagnosis.

▪ **Management of Diastolic Dysfunction:**

- Therapeutic options are limited for CHF with diastolic dysfunction.
- Drugs that are beneficial and should be used:
 - Beta blockers
 - Diuretics

- Drugs that are not beneficial and should NOT be used:
 - Digoxin
 - Spironolactone
- Drugs with uncertain role:
 - ACEI and ARBs
 - Hydralazine



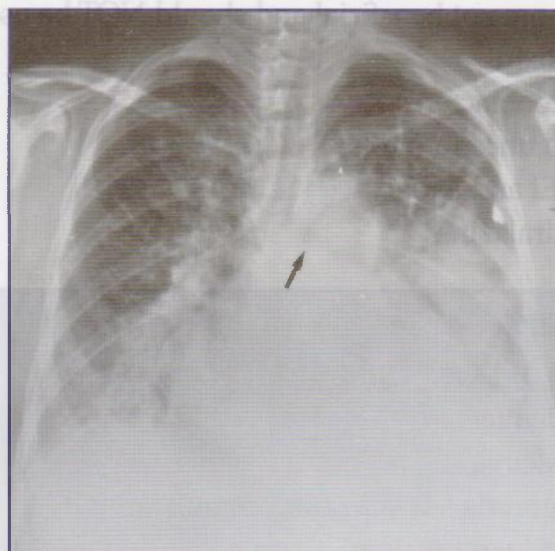
Clinical Pearl:

Complications of Heart Failure:

- Hypokalemia
- Hyperkalemia
- **Hyponatremia – it is a poor prognostic sign**
- Impaired liver function
- Thromboembolism
- Atrial & ventricular arrhythmias
- Sudden Cardiac Death:
 - It is the most common cause of death in CHF (occurs in up to 50% of patients)
 - It is often due to a ventricular arrhythmia

V. Acute Pulmonary Edema:

- It is the worst and most serious manifestation of CHF.
- It occurs when pulmonary hydrostatic pressure is more than pulmonary oncotic pressure.
- **Clinical Features:**
 - Sudden onset shortness of breath
 - Tachypnea; orthopnea
 - Pulmonary crackles
 - Oxygen saturation < 90% on air
 - CXR (**mnemonic ABCDE**):
 - A = Alveolar edema (Bat's wings appearance)
 - B = Kerley B-lines (interstitial edema)
 - C = Cardiomegaly
 - D = Dilated, prominent upper lobe vessels
 - E = Pleural Effusion



▪ **Treatment:**

Mnemonic: "LMNOP"

- Loop diuretic (furosemide 50 – 100 mg IV)
- Morphine (decreases symptoms, decreases afterload)
- Nitrates (IV glyceryl trinitrate):
 - 10 – 200 µg/min, titrated upwards every 10 minutes.
 - Titrate until clinical improvement occurs or systolic BP falls to < 110 mmHg.
- Oxygen:
 - High-flow, high-concentration
 - Non-invasive positive pressure ventilation (continuous positive airway pressure [CPAP] of 5 – 10 mmHg) by a facemask results in rapid improvement.
- Position i.e. sit the patient up (decreases preload)
- If no response, consider:
 - Inotropic agents (especially in hypotensive patients e.g. dobutamine)
 - Intra-aortic balloon pump (IABP)

Valvular Heart Diseases

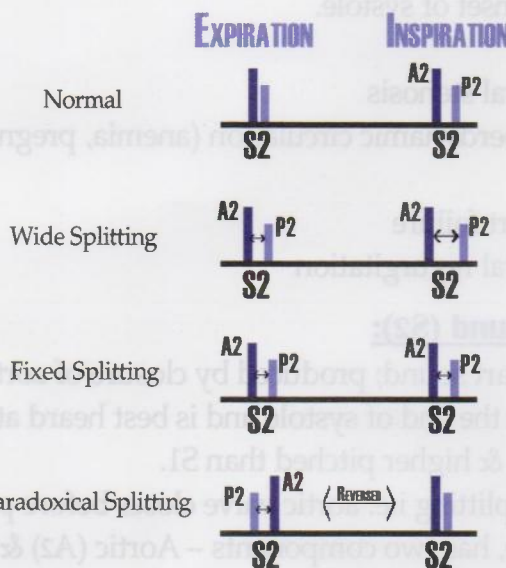
Heart Sounds:

▪ First Heart Sound (S1):

- Normal heart sound; produced by closure of mitral and tricuspid valves.
- Timing = onset of systole.
- Loud S1:
 - Mitral stenosis
 - Hyperdynamic circulation (anemia, pregnancy, thyrotoxicosis)
- Soft S1:
 - Heart failure
 - Mitral regurgitation

▪ Second Heart Sound (S2):

- Normal heart sound; produced by closure of aortic and pulmonary valve.
- It occurs at the end of systole and is best heard at left sternal edge.
- It is louder & higher pitched than S1.
- S2 shows splitting i.e. aortic valve closes before pulmonic valve.
- S2 therefore, has two components – Aortic (A2) & Pulmonic (P2).
- Normal Condition:
 - Inspiration = increases splitting
 - Expiration = minimizes splitting (so that it is heard as single sound)
- Wide Splitting:
 - It is an exaggeration of normal splitting.
 - It is seen in conditions that delay right ventricular emptying e.g.:
 - Pulmonary stenosis
 - Right bundle branch block
- Fixed Splitting:
 - It means that in both inspiration & expiration aortic valve closes before pulmonic
 - **It is seen in atrial septal defect (ASD).**
- Paradoxical Splitting:
 - It means that pulmonic valve closes before aortic valve.
 - It is seen in conditions that delay left ventricular emptying e.g.:
 - Aortic stenosis
 - Left bundle branch block



Second Heart Sound

Third Heart Sound (S3):

- It is a low-pitched, early diastolic sound.
- Timing = early in diastole just after S2.
- Best heard at the apex with bell of stethoscope.
- It occurs when rapidly rushing blood flow from the atria is suddenly decelerated by the ventricle when it reaches its elastic limit.
- Causes:
 - Normal before 40 years of age
 - Left ventricular failure
 - Mitral regurgitation
 - Tricuspid regurgitation
 - Acute aortic regurgitation



▪ **Fourth Heart Sound (S4):**

- It is a low-pitched, late diastolic sound.
- Timing = end of diastole just before S1.
- Best heard at left sternal border with bell of stethoscope.
- It is caused by forceful atrial contraction against a non-compliant ventricle
- It is always pathological.
- Causes:
 - LV hypertrophy – hypertension, aortic stenosis
 - RV hypertrophy – pulmonary hypertension, pulmonary stenosis

Acute Rheumatic Fever:

I. Introduction:

- Rheumatic fever is a systemic inflammatory disease, triggered by pharyngitis with Group-A beta-hemolytic streptococci (*streptococcus pyogenes*).
- It is the most common cause of acquired heart disease in childhood and adolescence.
- Pathogenesis:
 - It is a Type-II hypersensitivity reaction in which the antibodies that develop against M-proteins of streptococci cross-react with cardiac antigens.
 - It usually occurs in children 5 – 15 years.
 - It occurs 10 days to 6 weeks after pharyngitis.
 - Histologic Finding:
 - **Aschoff Bodies:**
 - These are pathognomonic and occur only in the heart.
 - They are composed of multinucleated giant cells surrounded by macrophages and T-lymphocytes.

II. Diagnostic Criteria:

- It requires the revised **Jones Criteria** for diagnosis.
- It is positive if there is evidence of recent streptococcal infection plus 2 Major criteria, or 1 Major + 2 Minor criteria.
- Evidence of Group A β -hemolytic streptococcal infection:
 - Positive throat culture
 - Rapid streptococcal antigen test
 - Elevated anti-streptolysin O (ASO) titers
 - Recent scarlet fever

<u>Major Criteria</u>	<u>Minor Criteria</u>
Migratory polyarthrititis	Fever
Carditis	Arthralgias
Subcutaneous nodules	Elevated ESR & CRP
Skin rash (erythema marginatum)	First-degree AV block
Sydenham chorea	Leukocytosis

III. Clinical Features:

▪ Migratory Polyarthrititis:

- It is the most common initial presentation of acute RF.
- It is characterized by acute, painful, asymmetrical and migratory arthritis.
- It involves the larger joints e.g. knees, ankles, elbows, wrists.
- **The pain characteristically responds to aspirin; if not, the diagnosis is in doubt.**

▪ Carditis:

- Acute RF causes "pancarditis" i.e. it can involve any of the three layers of the heart i.e.:
 - Pericarditis
 - Myocarditis – most common cause of death in acute attack.
 - Endocarditis:
 - Acute cases = mitral regurgitation
 - Chronic cases = mitral stenosis
 - It is associated with "**Carey Coomb's Murmur**":
 - **It is a soft mid-diastolic murmur.**
 - **It is due to valvulitis with nodules on mitral valve leaflets.**

▪ Subcutaneous Nodules:

- It occurs in 5 – 7% of cases.
- These are mobile, painless nodules on extensor surfaces of joints and spine.
- These typically appear > 3 weeks after the onset of disease.

▪ Erythema Marginatum:

- It occurs in < 5% of cases.
- The lesion is characterized by:
 - Red rash with raised edges and clear (pale) center.
 - It occurs mainly on trunk, thighs, and arms, but not on face.

▪ **Sydenham's chorea:**

- It is a late manifestation of acute RF; also known as **St. Vitus' dance**.
- It appears at least 3 months after acute attack.
- It is characterized by:
 - Emotional lability, followed by:
 - Reversible, rapid, involuntary, purposeless movements affecting all muscles.
 - Explosive and halting speech
 - 25% of affected patients will go on to develop chronic rheumatic heart disease.
 - Spontaneous recovery occurs within a few months.

IV. Investigations:

- CBC (leukocytosis)
- Raised ESR and C-reactive protein (CRP) – useful for monitoring progression of disease
- Evidence of preceding streptococcal infection:
 - Throat swab culture
 - Anti-streptolysin O antibodies (ASO titers):
 - > 200 U in adults
 - > 300 U in children
- CXR = cardiomegaly, pulmonary congestion
- ECG = first degree AV block
- Echocardiography = cardiac dilatation and valve abnormalities

V.

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Treatment:

▪ **Bed Rest:**

- It lessens joint pain and reduces cardiac workload.
- It should be continued until symptomatic improvement, settling of fever, WBC count, ESR and CRP.

▪ **Antibiotic for Acute Attack:**

- Single dose of benzyl penicillin 1.2 million U IM. OR
- Phenoxymethylpenicillin 250 mg 6-hourly per oral for 10 days.
- Penicillin-allergic Patients:
 - Erythromycin, Clarithromycin, Clindamycin, OR
 - Cephalosporin (cephalexin)

▪ **Analgesia:**

- Aspirin relieves pain of arthritis.
- Aspirin should be continued until ESR has fallen, then gradually tapered off.
- Corticosteroids should be used if Carditis and Arthritis are severe.
- Corticosteroids should also be continued until ESR has fallen, then tapered off.

▪ **Chorea:**

- Dopaminergic Blockers – Haloperidol, OR
- Benzodiazepines – Diazepam

▪ **Secondary Prevention:**

- Long-term antibiotic prophylaxis is required to prevent further attacks of rheumatic fever, but doesn't protect from infective endocarditis.
- Regimens:
 - Benzathine penicillin 1.2 million U IM every month, OR
 - Phenoxymethylpenicillin 250 mg 12-hourly per oral. OR
 - Penicillin-Allergic Patients:
 - Sulfadiazine 1 gm daily –OR
 - Erythromycin 250 mg 12-hourly daily
- Duration:

American Heart Association (AHA) Guidelines:

- If carditis + persistent valvular disease:
 - Continue until 10 years after the last episode, OR
 - Until at least 40 years of age (whichever is longer)
- If carditis, but no persistent valvular disease:
 - Continue until 10 years after the last episode, OR
 - Until age 21 years (whichever is longer)
- If no carditis = 5 year prophylaxis (until age 21) is sufficient.
 - Continue until 5 years after the last episode, OR
 - Until age 21 years (whichever is longer)



Clinical Pearl:

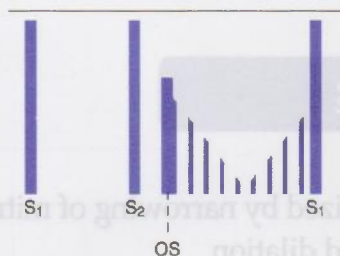
Rheumatic Heart Disease:

- Most common valve involved in rheumatic heart disease (acute & chronic) is the mitral valve.
- Acute it presents with MR, and chronically with MS.

Valvular Heart Diseases:

I. Mitral Stenosis:

- It is a condition characterized by narrowing of mitral valve orifice resulting in left atrial hypertrophy and dilation.
- **Causes:**
 - Rheumatic heart disease – most common cause
 - Mitral annular calcification
 - Valvulitis (SLE, amyloid, carcinoid)
 - Infiltrative disease (mucopolysaccharidoses)
- **Symptoms:**
 - Exertional dyspnea – most dominant symptom
 - Fatigue – due to low cardiac output
 - Left atrial enlargement:
 - Dysphagia (LA pressing on the esophagus)
 - **Ortner's syndrome** (hoarseness from LA pressing on recurrent laryngeal nerve)
 - Palpitations – due to atrial fibrillation:
 - AFib puts at risk of left atrial thrombosis
 - AFib puts at risk of systemic thromboembolism (stroke, limb ischemia)
 - Pulmonary hypertension leads to RV heart failure
 - All signs & symptoms increase with exercise and during pregnancy.
- **Signs:**
 - Malar facies:
 - It refers to bilateral dusky pink discoloration over upper cheeks.
 - It is due to low cardiac output, causing vasoconstriction and vascular stasis.
 - Apex beat = localized, and tapping
 - Heart sounds:
 - Loud S1
 - Loud P2 – if accompanied by pulmonary hypertension
 - Murmur:
 - **Low-pitched mid-diastolic murmur located at the apex.**
 - Best heard in left-lateral decubitus position during expiration using bell of stethoscope, and with exercise.



Mid-diastolic Murmur (OS = Opening Snap)

- **Opening Snap (OS):**
 - It is a high-pitched early diastolic sound at the apex.
 - It follows S2 and initiates the murmur.
 - Opening snap moves closer to S2 as the disease gets more severe.

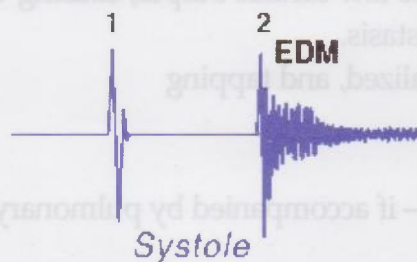


Clinical Pearl:

Signs Indicating Severe MS:

1. As the opening snap moves closer to S2, **MS gets** more severe.
2. The length (duration) murmur is **proportional** to severity.
3. The intensity of murmur is **NOT RELATED** to severity.
4. Presence of Graham-Steell murmur in the pulmonary area indicates pulmonary HTN and thus severe MS.
5. Malar facies indicates chronic severe MS, leading to reduced cardiac output & vasoconstriction.

- **Graham-Steell Murmur:**
 - It is a high-pitched decrescendo diastolic murmur.
 - It is best heard at the left upper sternal border in the 2nd intercostal space (i.e. pulmonary area).
 - It is associated with pulmonary regurgitation as a consequence of pulmonary hypertension.



Early diastolic murmur (Graham-Steell)

▪ **Investigations:**

- ECG= atrial fibrillation; bifid P-waves i.e. P-mitrale (due to left atrial hypertrophy)
- CXR:
 - Straightening of left heart border (atrial hypertrophy)
 - Elevation of left main-stem bronchus
 - Signs of pulmonary venous congestion.
- Echocardiography:
 - **Transthoracic echo (TTE) is the best initial test.**
 - Transesophageal echo (TEE) is more accurate.
 - Thickened immobile cusps
 - Narrow (fish-mouth) shaped orifice
 - Enlarged left atrium
 - Signs of RVF – in advanced disease

▪ **Management:**

Medical Management:

- Warfarin for atrial fibrillation to an INR of 2 to 3.
- Rate control of AFib (digoxin, beta-blockers, and calcium channel blockers).
- Diuretics and sodium restriction – for pulmonary edema & congestion
- Endocarditis prophylaxis not routinely recommended.

Balloon Valvuloplasty:

- It produces excellent results and indicated in severe disease.
- It is the treatment of choice if following criteria are fulfilled.
 - Significant symptoms
 - Isolated mitral stenosis
 - No mitral regurgitation
 - Mobile, non-calcified valve
 - LA free of thrombus

Valve Replacement:

- It is indicated in following conditions:
 - MS with mitral regurgitation
 - Immobile, calcified valve
 - LA thrombus despite anticoagulation

II. Mitral Regurgitation (MR):

- It is characterized by retrograde blood flow into the left atrium during systole, through a mitral valve that does not fit together.
- **Causes:**
 - Rheumatic fever prevalent countries = rheumatic heart disease (50%)
 - Rheumatic fever non-prevalent countries = mitral valve prolapse
 - Left-sided heart failure
 - SLE
 - Marfan's syndrome
 - Ehlers – Danlos syndrome
 - Acute Causes:
 - Endocarditis
 - Papillary muscle rupture (post MI)
 - Chordae Tendinae rupture
- **Symptoms:**
 - Acute MR:
 - It causes sudden rise in LA pressure, & therefore, symptomatic.
 - It presents with pulmonary edema, hypotension, and cardiogenic shock.
 - Chronic MR:
 - It causes gradual LA enlargement with little increases in pressure.
 - It is therefore asymptomatic for years, then presents with LV heart failure.
 - Thromboembolism is less common than MS.
 - Subacute infective endocarditis is much more common than MS
- **Signs:**
 - Apex beat = forceful, displaced with systolic thrill.
 - Heart sounds:
 - **Soft S1**
 - **Wide splitting of S2 – (due to early closure of aortic valve)**
 - **S3 – (due to LV dysfunction or increased blood flow across the mitral valve)**
 - Murmur:
 - **High-pitched, blowing pansystolic murmur at apex.**
 - **It radiates to the axilla and increases with expiration.**
 - It is increased with handgrip and decreased with Valsalva.



Pansystolic Murmur

- Carotid upstroke:
 - MR = carotid upstroke is brisk.
 - AS = carotid upstroke is diminished and delayed.
- **Investigations:**
 - ECG = bifid P-waves i.e. P-mitrale (due to left atrial hypertrophy) & LVH
 - CXR:
 - Enlarged LA
 - Enlarged LV
 - Pulmonary venous congestion
 - Pulmonary edema (acute MR)
 - Echocardiography is the best initial test.
 - Cardiac catheterization is the most accurate test.

Rx

Management:**Medical Management:**

- Afterload Reduction:
 - It is recommended in symptomatic patients, and those with hypertension.
 - Agent of choice – ACE-inhibitors & ARBs
- Atrial Fibrillation:
 - Anticoagulants if AFib is present.
 - Digoxin if AFib is present.

Surgical Management:

- Intra-aortic balloon pump (IABP) can be used as a bridge to surgery in acute MR.
- Valve replacement is indicated:
 - Ejection fraction is < 60%
 - Left-ventricular end systolic diameter (LVESD) is > 40 mm.
 - Do not wait for LVESD to become too large – damage will be irreversible.

III. Mitral Valve Prolapse (MVP):

- Also known as “Barlow Syndrome” or “Floppy Mitral Valve”.
- It is due to myxomatous degeneration of mitral valve.
- It is a condition characterized by retrograde blood flow into the left atrium during systole due to posterior bulging of anterior and posterior mitral leaflets into left atrium.
- **Causes:**
 - Idiopathic
 - Familial (autosomal dominant)
 - Marfan syndrome
 - Ehlers-Danlos syndrome
- **Presentation (3 P's):**
 - Pain (atypical chest pain) – is the most common symptom.
 - Palpitations
 - Panic attacks
 - **High-pitched, mid-systolic click** – is the most common sign
 - Diagnosis:
 - Echocardiography is investigation of choice.
 - Billowing of MV leaflet ≥ 2 mm above mitral annulus in parasternal long axis echo view.

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Management:

- Atypical chest pain and palpitations = beta blockers
- MVP + MR + AF = anticoagulation
- MVP + Severe MR = surgical repair (due to risk of sudden death)
- Endocarditis prophylaxis not recommended.

IV. Aortic Stenosis (AS):

- It is the most common of all valvular abnormalities.
- It is characterized by stenotic aortic valve, which causes obstruction to LV outflow, which results in left ventricular hypertrophy.
- **Causes:**
 - Congenital bicuspid AV – infants, children, adolescents
 - Calcified congenital bicuspid AV – young adults to middle-aged
 - Senile degenerative aortic stenosis – middle-aged to elderly
 - Rheumatic heart disease

■ Symptoms:

- Angina (most common)
- Syncope
- CHF (most serious, carries worse prognosis)
- Hemolytic anemia with schistocytes
- Sudden death

■ Signs:

- Apex beat = not displaced, sustained
- Heart sounds = soft A2 (i.e. aortic component of 2nd heart sound); S4.
- Pulse = low volume, slow-rising,
- Pulse pressure = narrow
- Murmur:
 - **Crescendo-decrescendo ejection systolic murmur at right 2nd intercostal space, radiating to carotids.**
 - Murmur is increased with passive leg raise (increased preload) and decrease with standing and Valsalva (decreased preload)



Crescendo-Decrescendo Murmur

Clinical Pearl:

Signs Indicating Severe AS:

1. Late-peaking murmur
2. Paradoxical splitting of S2
3. Inaudible A2
4. **Pulsus parvus et tardus** (pulses weak, with slow rise & small amplitude)

Rx

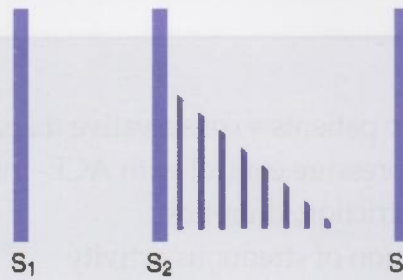
Management:

- Asymptomatic patients = conservative management
- Aortic Valve Replacement (AVR):
 - **AVR is the treatment of choice.**
 - **AVR is indicated in all symptomatic patients & asymptomatic with severe AS.**
 - **Old age is NOT a contraindication for valve replacement.**
 - Surgical AVR (SAVR)
 - patients with low – intermediate surgical risk
 - Transcatheter AVR (TAVR)
 - patients with prohibitive surgical risk and a predicted post-TAVR survival of > 12 months.
 - High-risk surgical patients
 - either TAVR or SAVR

V. Aortic Regurgitation (AR):

- It is a condition characterized by retrograde blood flow into the left ventricle due to an incompetent aortic valve or dilated valve ring.
- Causes:
 - Rheumatic heart disease – most common cause
 - Infection endocarditis (most common infectious cause)
 - Long-standing essential HTN
 - Aortic dissection
 - Chronic rheumatic fever
 - Takayasu arteritis
 - Syphilis
- Symptoms:
 - Acute = pulmonary edema, hypotension, cardiogenic shock
 - Chronic = asymptomatic until left ventricular failure develops, then CHF.
- Signs:
 - Apex beat = displaced, heaving, forceful
 - Pulse = large volume, collapsing
 - Murmur:
 - **High-pitched early diastolic decrescendo murmur at left sternal border.**
 - Increases with sitting forward, expiration and handgrip.

- Severity of AR is proportional to the duration of murmur.



Early Diastolic Murmur

- **Austin-Flint murmur:**
 - It is a mid-diastolic murmur heard at the cardiac apex in severe AR.
 - It is due to blood jets from regurgitation striking the anterior leaflet of the mitral valve, which results in premature closure of the "mitral leaflets".
- **Pulse Pressure:**
 - Pulse pressure is widened in chronic AR.
 - Pulse pressure is the difference between systolic and diastolic blood pressure.
 - Widened pulse pressure is because of:
 - Elevated stroke volume exists during systole
 - The incompetent aortic valve allows the diastolic pressure within the aorta to fall significantly.

Corrigan's pulse (water hammer pulse)	A bounding, forceful pulse with abrupt distention and quick collapse on palpation of arterial pulse (carotid, radial)
Duroziez's sign	Double murmur: <ul style="list-style-type: none"> Systolic murmur when the femoral artery is compressed proximally. Diastolic murmur when the femoral artery is compressed distally.
Muller sign	Systolic pulsation of the uvula
Musset's sign	Rhythmical bobbing movement of the head with each heartbeat.
Traube's sign	("pistol-shot" pulse) - Booming systolic and diastolic sounds auscultated over the femoral artery
Quincke's pulse	Visible pulsations of the fingernail bed with light compression of the fingernail

Rx

Management:

- Asymptomatic patients = conservative management:
 - Blood pressure control with ACE- inhibitors.
 - Salt restriction, diuretics
 - Restriction of strenuous activity
 - Annual echocardiogram
- Aortic valve replacement is the definitive treatment.
- AVR is treatment of choice in acute AR – a medical emergency!
- Aortic valve replacement is indicated in:
 - **Symptomatic patients**
 - **Asymptomatic patients:**
 - Ejection fraction is $\leq 55\%$
 - Left-ventricular end systolic diameter is ≥ 55 mm.

VI. Tricuspid Valvular Disease:

▪ Tricuspid Stenosis:

- Most common cause = rheumatic heart disease
- Main clinical feature = raised JVP with prominent “a” wave and slow “y” descent.
- Murmur = mid-diastolic murmur like MS, however, unlike MS:
 - It is best heard at left sternal border (not apex as in MS)
 - It is increased in intensity on inspiration (not expiration as in MS)

▪ Tricuspid Regurgitation:

- Most common cause = functional; from RV dilation (e.g. cor pulmonale, MI)
- Main clinical feature = “giant v wave” on JVP.
- Murmur = pansystolic murmur like MR, however, unlike MR:
 - It is best heard at left sternal border (not apex as in MR)
 - It is increased in intensity on inspiration (not expiration as in MR)

Clinical Pearl:

Murmurs:

- Left-sided murmurs (aortic and mitral valves) increases in intensity on expiration.
- Right-sided murmurs (tricuspid & pulmonic valves) increases in intensity on inspiration.

Infective Endocarditis (IE):

- It refers to microbial infection of the endothelium of the heart, including but not limited to the valves.

I. Risk Factors:

▪ **Abnormal Valve:**

- Prior endocarditis
- Rheumatic heart disease
- Mitral valve prolapse
- Aortic valvular disease
- Mitral valvular disease
- Artificial valves

▪ **Risk of Bacteremia:**

- Intravenous drug users
- Indwelling venous catheters
- Poor dentition
- Hemodialysis
- Diabetes
- Intra-cardiac devices (e.g. pacemakers, ICD)

▪ **Causative Organisms:**

- **Strep. Viridians** : most common overall cause of IE.
- **Staph. Aureus** : most common cause of IE in IV drug users
- **Staph. Aureus** : most common cause of acute IE
- **Staph. epidermidis** : most common cause of prosthetic valve endocarditis
- No organism : 10 % (culture-negative endocarditis).
- **HACEK** group (gram negative bacteria):
 - Haemophilus
 - Actinobacillus
 - Cardiobacterium
 - Eikenella
 - Kingella

▪ **Sites:**

- Mitral valve : most common overall valve involved in IE.
- Aortic valve : 2nd most common valve.
- Tricuspid valve : right-sided valves are commonly involved in IV drug abuse.

II. Types of Endocarditis:

Acute Endocarditis:

- Caused by high virulence organisms, involving a NORMAL valve.
- Produces large destructive vegetations that can extend onto the chordae.
- Prognosis = poor
- Agents:
 - **S. aureus (most common)**
 - Strep. pneumoniae, strep. Pyogenes.

Sub-acute Endocarditis:

- Caused by low virulence organism, involving a previously DAMAGED valve.
- Unlike acute IE, causes less valvular destruction.
- Unlike acute IE, vegetations have granulation tissue at their bases.
- Agents:
 - **Strep. Viridians i.e. strep. sanguis, & strep. mitis (most common)**
 - Streptococcus bovis
 - Enterococcus faecalis, Enterococcus faecium
 - Coxiella (Q fever)

III. Clinical Presentation:

Acute Endocarditis:

- Fever, chills, petechiae
- New murmur, change in murmur
- Clinical stigmata of chronic endocarditis is usually absent.
- Abscesses – on echocardiography

Sub-Acute Endocarditis:

- Fever, chills, night sweats, anorexia and weight loss.
- Anemia, splenomegaly and clubbing.
- Cardiac:
 - New murmur or a changing pre-existing murmur should raise the suspicion.
 - Conduction abnormalities; congestive heart failure
- Immune-Complex Vasculitis:
 - **"Roth spots"** (retinal hemorrhages + pale center)
 - **"Osler's nodes"** (painful subcutaneous nodules in the pulp of digits)
 - Glomerulonephritis
 - Arthritis

- Embolic Phenomenon:
 - Infarctions in different tissue sites (digits, brain, spleen)
 - Pulmonary emboli (if right-sided)
 - **"Splinter hemorrhages"** in fingernails.
 - **"Janeway's lesions"** (painless lesions on palms and feet)

IV. Diagnosis:

▪ **Blood Culture:**

- **It is the most accurate investigation.**
- It identifies the infection and guides antibiotic therapy.
- Obtain at least 3 (3 – 6) sets of cultures before commencing antibiotic therapy.
- Obtain cultures from different sites, ideally spaced ≥ 1 hour apart
- Follow strict aseptic measures, and avoid taking samples from in-dwelling lines.

▪ **Echocardiography:**

- It is key for:
 - Detecting & following the progress of vegetations.
 - Assessing valve damage
 - Detecting abscess formation
 - **Trans-esophageal echo (TEE) is more sensitive & specific than TTE.**
- Trans-thoracic echocardiography – if low-clinical suspicion
- Trans-esophageal echocardiography, if:
 - Moderate to high clinical suspicion
 - High-risk patient (prosthetic valve, prior IE)
 - TTE is non-diagnostic
 - TTE is negative, but endocarditis strongly suspected

▪ **Other Tests:**

- CBC, UCE, ESR, Urinalysis and urine cultures
- ECG – on admission & at regular intervals to assess for new conduction abnormalities

Modified Duke's Criteria:

- Definitive diagnosis: Two major; or 1 major + 3 minor; or 5 minor criteria
- Possible diagnosis: One major + One minor, or 3 minor criteria

Major Criteria	Minor Criteria
Positive blood cultures <ul style="list-style-type: none"> Typical organism from 2 cultures Persistent positive blood cultures taken > 12 hours apart ≥ 3 positive cultures taken over > 1 hour Endocardial involvement documented by: <ul style="list-style-type: none"> Echocardiographic findings, OR New valvular regurgitation 	<ul style="list-style-type: none"> Predisposing heart lesion IVD use Fever ($\geq 38^{\circ}\text{C}$) Embolic phenomenon Vasculitic phenomenon Suggestive echocardiographic findings Suggestive blood culture findings

V.

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Treatment:

Empiric antibiotic therapy:

- Acute bacterial endocarditis (ABE) = **Vancomycin + Gentamicin**
- Subacute bacterial endocarditis (SBE) = **Ceftriaxone + Gentamicin**, OR
Benzyl penicillin + Gentamicin, OR
Ampicillin (enterococcus) + Gentamicin
- Prosthetic valve IE: = **Vancomycin + Gentamicin + Rifampicin**
(oral) **Vancomycin + Cefepime + Gentamicin**

Specific Antibiotic Therapy:

Organism Specific Treatment	
Viridans streptococci	Ceftriaxone (4 weeks)
HACEK group	Ceftriaxone
S. aureus (penicillin-sensitive)	Oxacillin, Nafcillin, Cefazolin, Benzyl penicillin
S. aureus (resistant) – MRSA	Vancomycin
Staphylococcus epidermidis	Vancomycin
Enterococci	Ampicillin + Gentamicin
Fungal	Amphotericin + Valve replacement

- Subsequent antibiotic treatment is guided by culture results (table above)
- Antibiotic treatment is usually continued for at least 4 weeks.

▪ **Surgical Indications:**

- Heart failure due to valve damage—most common indication
- Failure of antibiotic therapy
- Prosthetic valves
- Large vegetations on left-sided heart valves
- Recurrent emboli while on antibiotics
- Abscess formation
- Fungal endocarditis

▪ **Endocarditis Prophylaxis:**

- Cardiac Conditions:
 - Prosthetic valve
 - Previous endocarditis
 - Cardiac transplant recipient with valvulopathy
 - Congenital cyanotic heart disease
- Procedures:
 - Dental procedures (with blood)
 - Respiratory procedures (incision & biopsy of respiratory mucosa)
 - Prophylaxis is NOT RECOMMENDED for:
 - Routine GI procedures (endoscopy, ERCP)
 - Routine GU procedures (cystoscopy, prostate biopsy)
 - Valvular heart disease, including MVP
 - Obstetric & gynecologic procedures
- Regimens:
 - No penicillin allergy = Amoxicillin 2g PO, 30 – 60 minutes before procedure
 - Penicillin allergy = Clindamycin 600 mg PO (IV, IM).

Cardiomyopathies

I. Dilated Cardiomyopathy (DCM):

- Also known as “congestive cardiomyopathy”.
- It is characterized by progressive cardiac dilation and contractile (**systolic dysfunction**).
- Ventricular mass is increased, but wall thickness is normal –to- reduced.
- **Etiology:**
 - Idiopathic (most common)
 - Genetics (≈ 25%):
 - Trait – autosomal dominant (most common)
 - Mutations – single-gene mutation (most common)
 - Coronary artery disease
 - Myocarditis
 - Alcohol
 - Thiamine deficiency (beriberi heart)
 - Peri-partum cardiomyopathy, which requires 3 criteria:
 - **CHF develops in the last month of pregnancy or within 5 months post-partum.**
 - **Ejection fraction of < 45%**
 - **No other cause of heart failure can be found.**
- **Clinical Findings:**
 - Men : Women (2: 1)
 - Signs and symptoms of left-sided and right-sided HF.
 - JVD; displacement of LV impulse
 - S3/S4 gallop
 - Complications:
 - Arrhythmias
 - Thromboembolism
 - Sudden cardiac death – can occur at any age
 - Death = progressive cardiac failure.
- **Diagnosis:**
 - CXR – moderate-to-severe cardiomegaly
 - ECG, echocardiography, and cardiac MRI.
 - Genetic testing is indicated if there is family history of DCM, and no other cause can be found.

R_x**Management:**

- Treatment is essentially the same as for CHF with systolic dysfunction:
- Medical Treatment:
 - ACEI& ARBs- reduces the risk of sudden arrhythmic death
 - Beta blockers – reduces the risk of sudden arrhythmic death
 - Spironolactone
 - Digoxin and diuretics for symptomatic relief only
- Surgical Treatment:
 - Biventricular Pacemaker when:
 - Ejection fraction of $\leq 35\%$ and
 - QRS duration of $\geq 120\text{ms}$.
 - Ventricular assist devices
 - Implantable cardiac defibrillators
 - Cardiac transplantation

II. Hypertrophic Cardiomyopathy (HCM):

- It is a group of inherited conditions that produce hypertrophy of myocardium.
- It is the most common type of cardiomyopathy.
- **Pathophysiology:**
 - Left ventricular outflow obstruction from asymmetric septal hypertrophy
 - Diastolic dysfunction – from increased chamber stiffness and impaired relaxation
 - Mitral regurgitation due to:
 - Systolic anterior motion (SAM) of anterior mitral valve leaflet
 - Papillary muscle displacement
- **Etiology:**
 - It is due to autosomal dominant mutations in cardiac sarcomere genes.
 - It is characterized by high penetrance, and variable expression.
 - Mutations:
 - β -myosin Heavy Chain:
 - Most common type of mutation.
 - Associated with severe ventricular hypertrophy.
 - Myosin-binding Protein C:
 - It presents late in life.
 - Associated with hypertension & arrhythmia.
 - Troponin Mutations:
 - Little ventricular hypertrophy, but marked myocardial fiber disarray.

- Associated with high risk of sudden death, exercise-induced hypotension.

▪ **Symptoms:**

- Exertional dyspnea
- Exertional chest pain
- Arrhythmias:
 - Palpitations
 - Syncope
 - Sudden cardiac death
 - Most common cause of sudden cardiac death in young athletes.

▪ **Signs:**

- **"Double apical pulsation"** – palpable 4th heart sound due to left atrial hypertrophy
- Pansystolic murmur at the apex – due to mitral regurgitation
- **"Jerky carotid pulse"** – due to rapid ejection and sudden obstruction of LV outflow during systole
- **"Ejection systolic murmur"** – due to LV outflow obstruction late in systole:
 - It is best heard at left lower sternal border (LLSB).
 - Murmur is increased by anything that decreases LV chamber size.
 - Increasing Preload:
 - It increases LV size & thus decreases outflow obstruction (squatting, leg raise)
 - It therefore DECREASES murmur intensity.
 - Decreasing Preload:
 - It decreases LV size & thus increases outflow obstruction (Valsalva, standing).
 - It therefore INCREASES murmur intensity.
 - Sustained Handgrip:
 - It increases afterload (decreased gradient across aortic valve).
 - It therefore decreases murmur intensity.

▪ **Investigations:**

- ECG:
 - Left ventricular hypertrophy
 - ST and T-wave changes
 - Septal Q waves in the inferior & lateral leads are common.

- Echocardiography:
 - Asymmetrical (septal) LV hypertrophy
 - Systolic anterior motion of mitral valve
 - Vigorously contracting ventricle
- Cardiac Catheterization:
 - It is the most accurate test.
 - It allows precise measurement of gradients of pressure across the chamber.


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Management:

- Chest pain and dyspnea:
 - Beta-blockers – preferred first-line agents
 - Alternatives: CCBs, and Disopyramide
- Arrhythmias = amiodarone
- Atrial fibrillation = anticoagulation
- Syncope = implantable defibrillators
- Drugs to avoid = digoxin, vasodilators
- If medical therapy fails:
 - Alcohol septal ablation
 - Surgical myomectomy
 - Dual-chamber pacing
 - Transplantation



Clinical Pearl:

Indications for Implantable Cardiac Defibrillator in HCM:

- To prevent the risk of sudden cardiac death ICD should be considered in:
 - Family history of sudden cardiac death
 - Unexplained (recurrent) syncope
 - Previous history of cardiac arrest
 - Previous history of sustained ventricular tachycardia
 - Exercise-induced hypotension
 - Increased in LV wall thickness (≥ 30 mm)

III. Restrictive Cardiomyopathy:

- It is characterized by impaired ventricular filling due to decreased compliance in absence of pericardial disease.
- **Etiology:**
 - Autoimmune = scleroderma, polymyositis, dermatomyositis
 - Infiltrative diseases = amyloidosis, sarcoidosis, hemochromatosis
 - Storage diseases = Gaucher's, Fabry's, Hurler's, glycogen storage diseases
 - Endomyocardial = endomyocardial fibrosis, metastatic cancer, carcinoid, radiation
- **Clinical Features:**
 - Right-sided > Left-sided heart failure
 - Peripheral edema > pulmonary edema
 - Thromboembolic events
 - Poorly tolerated tachyarrhythmias
 - Signs:
 - "Friedrich's sign" = elevated JVP with diastolic collapse
 - "Kussmaul's sign" = elevation of JVP on inspiration
 - Hepatomegaly, ascites, and peripheral edema
 - 3rd and 4th heart sounds may be audible.
- **Diagnosis:**
 - CXR – normal ventricular chamber size, enlarged atria
 - ECG – low-voltages, conduction abnormalities, arrhythmias
 - Echo:
 - Symmetric wall thickening
 - Increased RA & LA size with normal ventricular size.
 - Cardiac MRI
 - Cardiac catheterization
 - Endomyocardial biopsy

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Treatment:

- There is no specific treatment.
- Treat the underlying cause
- Heart failure and embolic manifestations should be treated.
- Transplantation – in severe cases.

Diseases of Pericardium

I. Acute Pericarditis:

▪ Causes:

- Infectious pericarditis:
 - Viral – most commonly by Coxsackievirus and echovirus
 - Bacterial; Tuberculous; Fungal
- Post-MI pericarditis (Dressler syndrome)
- Uremic pericarditis – in patients with advanced renal failure
- Post-radiotherapy
- Post-surgery
- Autoimmune:
 - Collagen-Vascular – e.g. rheumatoid arthritis, SLE
 - Drug-induced – e.g. procainamide, hydralazine, cyclophosphamide
- Malignant pericarditis:
 - Primary tumors of heart – e.g. mesothelioma
 - Metastatic pericarditis – e.g. breast cancer, lymphoma, leukemia

▪ Clinical Features:

- Chest pain:
 - **Chest pain is pleuritic – aggravated with deep breathing (unlike MI)**
 - **Chest pain is positional:**
 - Aggravated by lying supine, coughing, & deep inspiration
 - Relieved by sitting up and leaning forward.
- **“Pericardial Friction Rub”:**
 - **It is diagnostic of pericarditis; usually heard in systole.**
 - It is caused by friction between visceral and parietal pericardial surfaces.
 - It is high-pitched, superficial, scratchy sound.
 - It is heard best during expiration with patient sitting up and with stethoscope placed firmly against chest.

▪ Diagnosis & Management:

- ECG:
 - **Widespread ST-elevation with upward concavity**
 - **PR-interval depression – very specific indicator**
- Treatment:
 - Aspirin (600 mg, 6 times daily)
 - NSAIDs (indomethacin 25 mg x 3 daily)
 - Steroids

- Purulent Pericarditis:
 - Antibiotics
 - Pericardiocentesis, if necessary, surgical drainage
- Tuberculous Pericarditis:
 - Anti-tuberculous chemotherapy, PLUS
 - 3 – month course of steroids

II. Pericardial Effusion & Cardiac Tamponade:

- Pericardial effusion = collection of fluid within the potential space of the serous pericardial sac.
- Cardiac tamponade refers to acute heart failure due to compression of heart by a large or rapidly developing effusion.
- **Clinical Features:**
 - Heart sounds are soft and distant
 - Apex beat is obscured
 - Friction rub – due to pericarditis (in early stages)
 - **Ewart's sign** – area of dullness to percussion below the angle of left scapula (due to compression of base of left lung by effusion).
 - As effusion worsens, signs of cardiac tamponade may become evident:
 - Cardiogenic shock without pulmonary edema
 - **Beck's triad** = distant heart sound, raised JVP, and hypotension
 - **Pulsus paradoxicus** – decrease in systolic BP by ≥ 10 mmHg during inspiration
 - Tachypnea, but clear lungs
- **Diagnosis:**
 - ECG:
 - Low-voltage QRS complexes
 - **Electrical alternans** – i.e. QRS complexes alternate in amplitude due to to-and-fro motion of heart within the fluid-filled pericardial sac
 - CXR:
 - Large, globular heart with sharp outlines
 - Typically, the pulmonary veins are not distended
 - Echocardiography:
 - It is the most useful technique.
 - It demonstrates the site, size, and presence of effusion and tamponade
- **Management:**
 - Treat the underlying cause.
 - Pericardiocentesis:
 - Indications:
 - Pericardial effusion – diagnostic purposes

- Cardiac tamponade – to relieve the pressure
- Technique:
 - It is done under echocardiographic guidance.
 - Site of insertion: medial to cardiac apex or below the xiphoid process
 - It is directed upwards towards the left shoulder.

III. Constrictive Pericarditis:

- It is due to progressive thickening, fibrosis, and calcification of pericardium.
- It is characterized by rigid pericardium that limits diastolic filling, resulting in increased systemic venous pressures.

Causes:

- Tuberculous pericarditis – most common
- Hemo-pericardium
- Viral pericarditis
- Rheumatoid arthritis
- Radiation
- Uremia
- Post-cardiac surgery

Clinical Features:

- Right-sided failure > left-sided failure
- Fatigue
- Hepatomegaly, ascites, peripheral edema
- **Elevated JVP with rapid “y” descent**
- **Kussmaul’s sign – elevation of JVP on inspiration**
- **Pulsus paradoxus – decrease in systolic BP by ≥ 10 mmHg during inspiration**
- **Pericardial knock – corresponds to the abrupt cessation of the ventricular filling**

Diagnosis:

- CXR = small heart (heart failure); pericardial calcifications
- ECG = low-voltage QRS complexes
- Echo = thickened, calcified pericardium

Treatment:

- Treat the underlying condition
- Diuretics – for fluid-overload symptoms
- Pericardiectomy:
 - It refers to surgical resection of the pericardium.
 - It leads to dramatic improvement, but carries a high morbidity.

Diseases of Aorta & Hypertension

I. Abdominal Aortic Aneurysm (AAA):

- It refers to an abnormal dilatation of the abdominal aortic wall.
- **Risk Factors:**
 - Male gender
 - Family history
 - Hypertension
 - Hyperlipidemia
 - Smoking
- **Clinical Features:**
 - Median age at presentation is:
 - 65 years for elective cases
 - 75 years for emergency cases
 - Usually asymptomatic; found incidentally
 - Central abdominal pain with pulsatile mass
 - Complications:
 - Rupture (constant abdominal pain, hemorrhagic shock)
 - Thromboembolic ischemic events
- **Diagnosis:**
 - Contrast – CT scan
 - Abdominal ultrasound:
 - Screening and surveillance test of choice for AAA.
 - Screening guidelines:
 - All men > 60 years with family history of AAA
 - All men 65 – 75 years with prior tobacco use

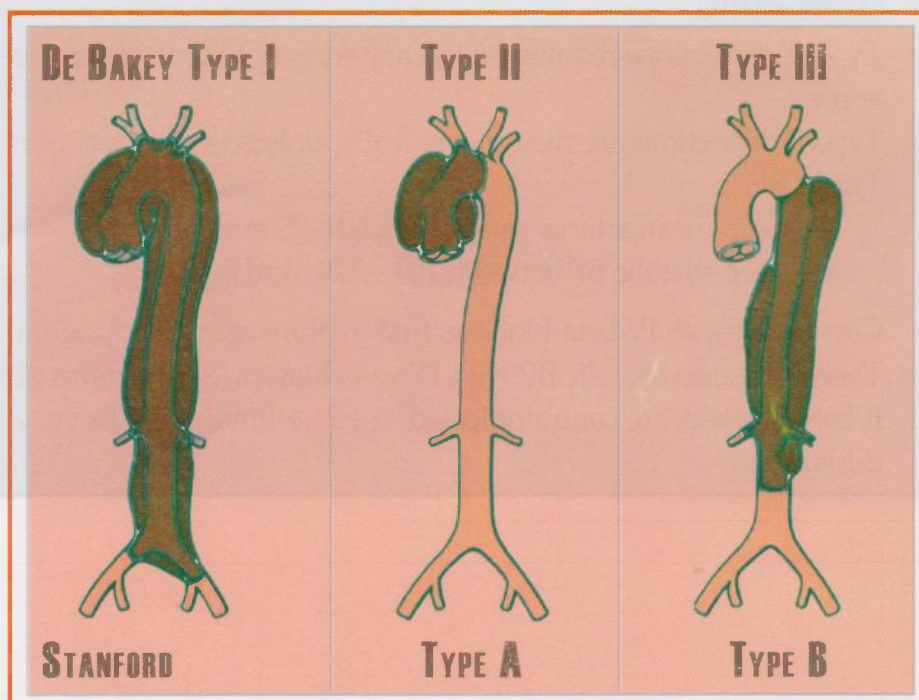
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Management:

- Indications for repair:
 - Asymptomatic AAA > 5.5 cm
 - Rapidly enlarging AAA
 - Symptomatic AAA, regardless of size
 - Distal embolization, regardless of size
- Modes of repair:
 - Endovascular aneurysm repair (EVAR) – ideal for infra-renal AAA.
 - Open surgical repair:
 - Mode of choice for elective & emergency cases
 - 30-day Mortality:
 - 5 – 8% = elective asymptomatic cases
 - 10 – 20% = emergency symptomatic cases
 - 50% = ruptured cases

II. Aortic Dissection:

- It is characterized by aortic intimal tear resulting in extravasation of blood into aortic media, which is then split into two layers, creating a false lumen alongside true lumen.
- **Risk Factors:**
 - Hypertension – 80% cases
 - Aortic atherosclerosis
 - Aortic coarctation
 - Marfan's syndrome
 - Ehlers-Danlos syndrome
 - Fibromuscular dysplasia
 - Pregnancy
 - Trauma
 - Iatrogenic – e.g. cardiac catheterization
- **Classification:**
 - Stanford A = Proximal
 - Stanford B = Distal
 - DeBakey-I = ascending + descending aorta
 - DeBakey-II = ascending aorta only
 - DeBakey-III = descending aorta only



▪ **Clinical Features:**

- Men > women
- Peak incidence is in 6th and 7th decade
- Pain:
 - Ascending aorta = anterior chest pain; sudden onset, severe and tearing
 - Descending aorta = inter-scapular pain; sudden onset, severe and tearing
- Syncope
- Congestive heart failure
- Cerebrovascular accident
- Asymmetry of pulses (brachial, carotid, or femoral)
- Hypertension
- Hypotension and shock (due to tamponade, MI, rupture)

▪ **Diagnosis:**

- CXR:
 - Mediastinal widening
 - Distortion of aortic knuckle
- Trans-esophageal echo
- CT and MRI angiography – highly specific and sensitive

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Treatment:

- Type-A dissections require emergency surgery to replace the ascending aorta
- Type-B dissections are treated medically, unless there is risk of rupture.
- Target BP:
 - Keep mean arterial pressure of 60 – 75 mmHg.
 - Keep systolic BP between 100 – 120 mmHg.
- Control BP with IV beta-blockers first to blunt reflex tachycardia.
- Then decreased systolic BP with IV vasodilators (e.g. nitroprusside)
- If beta-blockers are contraindicated, use rate-limiting CCBs i.e. verapamil, diltiazem.

III. Hypertension:

- It is defined as systolic BP >140 mm Hg and diastolic BP >90 mm Hg for a sustained period.
- Blood pressure should be determined by making ≥ 2 measurements separated by > 2 minutes.
- **Classification:**

<u>Category</u>	<u>Systolic (mmHg)</u>	<u>Diastolic (mmHg)</u>
Optimal	<120	< 80
Normal	< 130	< 85
HTN – Grade-I	140 – 159	90 – 99
HTN – Grade-II	160 – 179	100 – 109
HTN – Grade-III	≥ 180	≥ 110

- **Etiologies:**
 - Essential HTN:
 - It accounts for 95% of cases of HTN.
 - Onset is 25 – 55 years
 - Positive family history
 - Unclear mechanism
 - Secondary HTN:
 - Consider if patient < 20 or > 50 years
 - Consider if sudden, severe, refractory HTN
 - Renal (most common):
 - Renal parenchymal (e.g. glomerulonephritis, DM, polycystic kidney)
 - Renovascular (e.g. renal artery stenosis, polyarteritis nodosa)
 - Endocrine:
 - Cushing syndrome
 - Pheochromocytoma
 - Acromegaly
 - Hypothyroidism – diastolic HTN
 - Hyperthyroidism – systolic HTN
 - Medications:
 - Oral contraceptives; steroids, NSAIDs
 - Erythropoietin; cyclosporine
 - Other Causes:
 - Coarctation of aorta
 - Polycythemia vera

▪ Complications:

- Neurologic:
 - Transient ischemic attack; Stroke
 - Ruptured aneurysms
- Cardiac:
 - CAD, LVH, CHF
 - Atrial fibrillation is common
- Vascular = aortic dissection; aortic aneurysm
- Renal = proteinuria; renal failure
- Retinopathy:
 - Grade – I = arteriolar thickening and narrowing
 - Grade – II = grade I + constriction of veins at arterial crossings i.e. "Arteriovenous nipping".
 - Grade – III = grade II + retinal hemorrhages and exudates
 - Grade – IV = grade III + papilledema

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Management:

- Goal:
 - Blood pressure < 140/90 mmHg
 - Blood pressure < 130/80 mmHg if DM or renal disease
- Lifestyle modifications:
 - Weight loss; goal BMI = 18.5 – 24.9
 - Aerobic exercise: ≥ 30 min exercise/day, ≥ 5 days/week
 - Diet rich in fruits and vegetables, low in saturated and total fat
 - Sodium restriction to ≤ 2.4 g/day and ideally ≤ 1.5 g/day
 - Limit alcohol consumption
- Pharmacologic Treatment:
 - Offer pharmacologic treatment to patients with:
 - BP > 160/100 mmHg, OR
 - Isolated systolic HTN i.e. systolic BP > 160 mmHg, OR
 - BP > 140/90 mmHg + cardiovascular disease, or target organ damage (e.g. nephropathy, TIA, retinopathy)
 - Choice of therapy is controversial, concomitant disease may help guide.
 - Uncomplicated HTN = thiazide diuretics, better than ACEI or CCBs
 - Benign prostatic hyperplasia = alpha-blocker e.g. prazosin
 - Angina = beta-blockers or CCBs
 - Post-MI = beta-blockers; ACEI
 - CHF = ACEI/ARBs; beta-blockers, diuretics, aldosterone antagonist
 - DM = ACEI or ARBs (prevent progression to diabetic nephropathy)

- Chronic kidney disease = ACEI or ARBs
- Recurrent stroke prevention = ACEI
- Stepwise Approach:
 - Step 1:
 - Patient < 55 years = start ACEI
 - Patient > 55 years or black (African or Caribbean) = start thiazide or CCB
 - Step 2: = ACEI + Thiazide, OR, ACEI + CCB
 - Step 3: = ACEI + Thiazide + CCB
 - Step 4: = ACEI + Thiazide + CCB, plus
 - Another diuretic, OR
 - Alpha-blocker, OR
 - Beta-blocker

▪ **Hypertensive Crisis:**

- Hypertensive Urgency:
 - It refers to systolic BP > 180 or diastolic BP > 120 with no target-organ damage
- Hypertensive Emergency:
 - It refers HTN + target-organ ischemia and damage, like:
 - CNS = ischemic stroke, hemorrhagic stroke, encephalopathy, papilledema
 - CVS = acute coronary syndrome, acute pulmonary edema, aortic dissection
 - Renal = proteinuria, hematuria, acute renal failure, microangiopathic hemolytic anemia, pre-eclampsia, eclampsia

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Management:

- Hypertensive urgency:
 - Lower BP "in hours" using per oral agents
 - Achieve normal BP in 1 – 2 days.
 - Agents = captopril, labetalol, clonidine, hydralazine
- Hypertensive emergency:
 - Lower mean arterial pressure by 25% "in mins to 2 hrs" with IV agents.
 - Goal diastolic BP < 110 mmHg within 2 – 6 hours.
 - Agents:
 - Nitroprusside 0.25 – 10 µg/kg/min
 - Nitroglycerin 17 – 1000 µg/min
 - Labetalol: 20 mg load, followed by 20 – 80 mg IV every 10 minutes.

Congenital Heart Diseases (CHD)

Introduction:

- It is the most common type of heart disease among children.
- It mostly caused by faulty embryogenesis during gestational weeks 3 – 8.
- Trisomy 21 is the most common genetic cause of congenital heart disease.
- Well-defined genetic or environmental influences are identifiable in only about 10% of cases of congenital heart disease.

I. Right-to-Left Shunt:

- It refers to malformations in which the blood from right side of the heart enters the left side.
- It results in cyanotic congenital heart disease (because de-oxygenated blood from right side enters the left side by bypassing oxygenation in the lungs).
- A right-to-left shunt occurs when:
 - When there is a shunt (opening) between the atria, ventricles, or great vessels. PLUS:
 - Right heart pressure > left heart pressure, OR:
 - The shunt has a one-way valve opening
- Presentation:
 - Cyanosis
 - Paradoxical embolism
 - Clubbing of tips of fingers and toes
 - Polycythemia
- Examples "4Ts":
 - Tetralogy of Fallot
 - Transposition of the great vessels
 - Truncus arteriosus
 - Tricuspid atresia

(i). Tetralogy of Fallot:

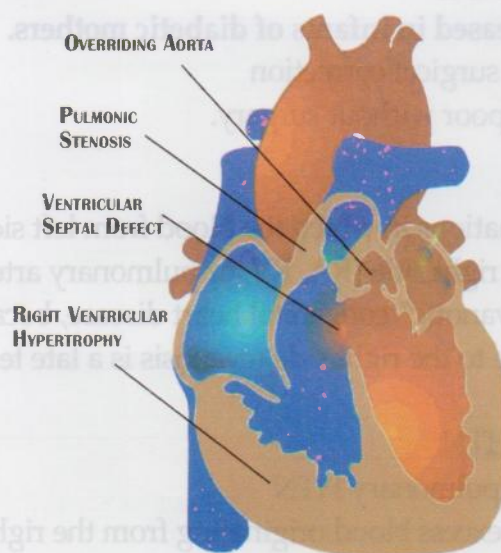
- Components:
 - It is the most common cyanotic heart lesion.
 - It consists of (PROV):
 - Pulmonary outflow obstruction
 - Right ventricular hypertrophy
 - Overriding aorta:
 - The aortic valve forms the superior border of VSD.
 - The aortic valve therefore overrides the defect and both ventricular chambers.
 - Ventricular septal defect (VSD)

- **Clinical Findings:**

- Cyanosis:
 - It is the most common symptom.
 - It may not be present in neonates (develops only when RV pressure \geq LV)
- **"Fallot Spells"** – cyanosis after feeding or crying
- Older Children:
 - Failure to thrive
 - Digital clubbing
 - Polycythemia
 - **"Tet Spells (Fallot's sign)"**:
 - To relieve symptoms after exertion, the child will squatting.
 - Squatting will increase systemic vascular resistance (SVR) i.e. afterload, which helps shunt blood from RV to the lungs instead of aorta (decreases right-to-left shunting).
- **Murmur – Ejection systolic murmur in the pulmonary area (left upper sternal border)**

- **Diagnosis:**

- Echocardiography:
 - It is the diagnostic modality of choice.
 - It can clearly define all the four abnormalities.
- ECG = right axis deviation + right ventricular hypertrophy
- Chest X-ray:
 - **Hypertrophied right ventricle (boot-shaped heart) – hallmark feature**
 - **Diminished vascularity in lungs (abnormally small pulmonary artery)**



Tetralogy of Fallot

▪ **Treatment:**

- Definitive Surgery:
 - It involves total correction of the defects.
 - It should be undertaken prior to the age of 5 years.
 - Studies have shown that surgery is preferably done at or about 12 months of age.
- Palliative Surgery (Blalock – Taussig Shunt):
 - It is done when pulmonary arteries are too hypoplastic.
 - It involves creating an anastomosis b/w pulmonary artery & subclavian artery.
 - This improves pulmonary blood flow & development (for later definitive correction)

(ii). Transposition of the Great Arteries (TGA):

- It is an anomaly characterized by:
 - Aorta arising from the right ventricle
 - Pulmonary artery arising from the left ventricle.
 - Aorta lies anterior and to the right of the pulmonary artery.
 - This, therefore, results in:
 - Separation of the systemic and pulmonary circulations - incompatible with life
 - Post-natal survival requires mixing of blood by a VSD, ASD, or PDA.
- Clinical Features:
 - **It is the most common cyanotic lesion presenting in the immediate newborn period.**
 - **Risk is increased in infants of diabetic mothers.**
 - Treatment = surgical correction
 - Prognosis = poor without surgery.

II. Left-to-Right Shunt:

- It refers to malformations in which the blood from left side of the heart (LA, LV, or aorta) enters the right side (RA, RV, or pulmonary artery).
- It is also called “acyanotic” congenital heart disease, because oxygenated blood enters from left side to the right side (cyanosis is a late feature).
- Presentation:
 - Pulmonary HTN
 - RVH due to pulmonary HTN
 - LVH due to excess blood originating from the right side of the heart

- Reversal of shunt (RV pressure overrides LV pressure) – Eisenmenger's syndrome
- Late cyanosis
- Examples:
 - Atrial Septal Defect (ASD)
 - Ventricular Septal Defect (VSD)
 - Patent Ductus Arteriosus (PDA)
 - Atrioventricular Septal Defect (AVSD)

(i). Ventricular Septal Defect:

- It refers to direct communication between the ventricular chambers.
- **It is the most common congenital heart disease (1: 500 live births).**
- Site of defect:
 - Most common site: peri-membranous i.e.:
 - At the junction of membranous & muscular portion of interventricular septum
- **Pathophysiology:**
 - It is a left-to-right shunt (i.e. blood flows from high-pressure LV into low-pressure RV).
 - This results in increased pulmonary blood flow.
 - The shunt remains left-to-right as long as pulmonary vascular resistance (PVR) is < systemic vascular resistance (SVR).
 - The shunt reverses to right-to-left once PVR is > SVR once pulmonary hypertension develops – **"Eisenmenger's syndrome"**
- **Clinical findings:**
 - A Small shunt produces no symptoms
 - A large shunt with normal PVR:
 - Congestive heart failure
 - Growth failure; Recurrent respiratory tract infections
 - A large shunt with high PVR:
 - Shortness of breath
 - Dyspnea on exertion
 - Chest pain,
 - Syncope, Cyanosis
 - Signs:
 - Sternal lift (RV heave)
 - Murmur:
 - **Harsh, blowing, holosystolic murmur with thrill.**

- At fourth left intercostal space
- The smaller the defect the louder the murmur.
- Murmur decreases with Valsalva & handgrip.

▪ **Diagnosis:**

- ECG – biventricular hypertrophy
- CXR – Enlargement of pulmonary artery (pulmonary plethora)
- Echocardiography – diagnostic
- Cardiac MRI, Cardiac catheterization

▪ **Treatment:**

- Small asymptomatic defects = no treatment
- Congestive heart failure = digoxin, diuretics, surgery (refractory cases)
- Surgical repair is indicated when:
 - Pulmonary flow to systemic flow is $> 1.5: 1$ ($>50\%$)
 - Patients with infective endocarditis
- Eisenmenger's Syndrome:
 - **Surgical repair is contraindicated in fully developed Eisenmenger's syndrome.**
 - Heart-lung transplantation is the only effective treatment

(ii). Atrial Septal Defect:

- It refers to direct communication between atrial chambers.
- It results in a left-to-right shunt, because:
 - Pulmonary vascular resistance (PVR) is $<$ systemic vascular resistance (SVR)
 - Compliance of right ventricle is much greater than that of the left ventricle.

▪ **Types:**

- Secundum ASD:
 - Most common type – 90% of all ASDs
 - Defect is due to deficient or fenestrated oval fossa (foramen ovale).
- Primum ASD:
 - Defect is adjacent to atrioventricular septum.
 - Associated with a "cleft anterior mitral leaflet".

▪ **Clinical findings:**

- It is the most common congenital heart disease in adults.

- It usually doesn't become symptomatic before age 30.
- Symptoms:
 - Incidental detection on routine clinical examination
 - Dyspnea, chest infections, cardiac failure, and arrhythmias.
- Signs:
 - **Systolic ejection murmur along left sternal border** (from increased pulmonary flow)
 - **Wide fixed splitting of S2.**
- **Diagnosis:**
 - CXR - cardiomegaly, enlargement of pulmonary artery, pulmonary plethora
 - ECG - incomplete RBBB (RV depolarization is delayed due to ventricular dilatation).
 - Echo - most accurate investigation
- **Management:**
 - Surgical correction:
 - **If pulmonary blood flow to systemic blood flow is $> 1.5: 1$ ($> 50\%$)**
 - Excellent prognosis (if pulmonary hypertension hasn't developed).



Clinical Pearl:

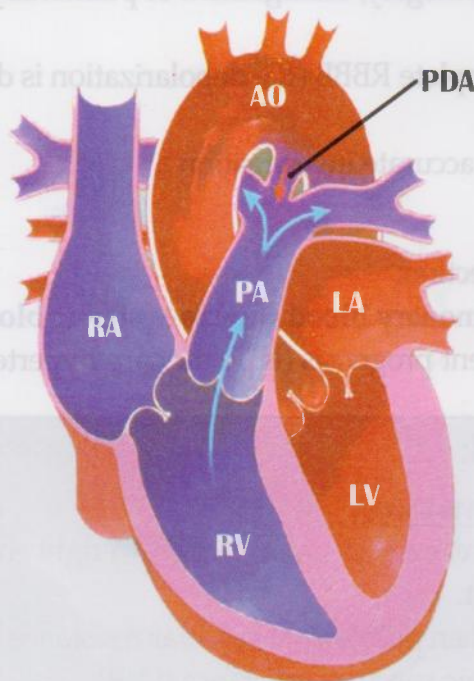
Eisenmenger's Syndrome:

- It refers to reversal of untreated left-to-right shunt into right-to-left shunt.
- It occurs when pulmonary vascular resistance (PVR) is more than systemic vascular resistance (SVR).
- It is characterized by cyanosis, clubbing and polycythemia

(iii). Patent Ductus Arteriosus:

- It is communication between the aorta and pulmonary artery because the ductus arteriosus remains open after birth.
- It results in left-to-right shunt, since pressure in the aorta is higher than that in pulmonary artery.
- **Pathophysiology:**
 - The ductus arteriosus connects the pulmonary artery with the aorta.
 - Prenatally, it is a vital structure, allowing blood from pulmonary artery in to the aorta (bypassing the lungs, which are not fully functional)
 - Ductus arteriosus closes after birth, in the first days of life.

- Closure is triggered by the postnatal **pO₂ increase** due to the breathing of the newborn.
- **Clinical Features:**
 - It is associated with prematurity and congenital rubella infections.
 - It first causes left-to-right shunt resulting in pulmonary HTN and late cyanosis
 - Murmur:
 - **Continuous machinery murmur**
 - **Best heard in 2nd left intercostal space below the clavicle.**



PDA (PA = Pulmonary Artery, AO = Aorta)

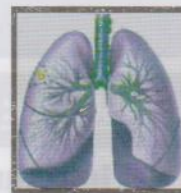
- **Treatment:**
 - Pharmacologic Closure (Neonates):
 - Prostaglandin synthase inhibitors – indomethacin, ibuprofen
 - Used in the first week of life (when the ductus is structurally intact)
 - Surgical Correction:
 - Surgical ligation is indicated in the absence of pulmonary hypertension.
 - Surgery is contraindicated in presence of pulmonary HTN & Eisenmenger's syndrome.
 - Keeping PDA Open:
 - Prostaglandin E1 can be used to keep the PDA open.
 - Open PDA may be vital in other cardiac anomalies (e.g. TGA).

Coarctation of the Aorta:

- It refers to segmental narrowing of the aorta.
- It affects males twice as often as females.
- **Associations& Types:**
 - Bicuspid aortic valve
 - Berry aneurysm of cerebral circulation
 - Patent ductus arteriosus
 - Turner's syndrome – coarctation is the most common cardiac defect
 - Most common site:
 - The site where ductus arteriosus (ligamentum arteriosum) joins the aorta i.e.
 - At the isthmus just below the origin of left subclavian artery.
 - Types:
 - Pre-ductal Type:
 - Narrowing of aorta is proximal to the ductus arteriosus.
 - Also known as "Infantile Type".
 - Post-ductal Type:
 - Narrowing of aorta is distal to the ductus arteriosus.
 - Also known as "Adult Type".
- **Clinical findings:**
 - Hypertension in upper extremities
 - Hypotension and weak pulses in lower extremities
 - "Radio-Femoral Delay" – femoral pulse is weak & delayed compared to radial pulse
 - Systolic murmur – best heard over the back
- **Diagnosis:**
 - MRI – most accurate method
 - Chest X-ray:
 - Notching of the inferior border of the ribs – due to arterial collaterals
 - "3 – Sign":
 - Indentation of aorta at the site of coarctation
 - Dilation before & after stenosis (coarctation)
- **Treatment:**
 - Surgical decompression:
 - It is the standard treatment.
 - It should ideally be performed early in childhood, to avoid persistent HTN.

Chapter 6

PULMONOLOGY



Pulmonary Function Tests

I. Definitions:

- Total Lung Capacity (TLC):
 - It is the volume of gas in the lungs after maximal inspiration.
 - Normal value is 80 – 120% predicted.
- Residual Volume (RV):
 - It is the volume of gas remaining in lungs after forced maximal expiration.
 - Normal value is 80 – 120%.
- Vital Capacity (VC):
 - It is the volume of gas exhaled with maximal forced expiration.
 - $TLC = RV + VC$ or $VC = TLC - RV$
- FEV₁ to FVC is ratio:
 - Forced expiratory volume (FEV) measures air movement in and out of lungs.
 - Forced expiratory volume at 1 second is FEV₁.
 - FVC is forced vital capacity.
 - FEV₁ to FVC ratio is 80%.
- Diffusion Capacity of Carbon Monoxide (DLCO):
 - It determines how well oxygen passes from alveolar space of lungs into blood.
 - In obstructive lung disease decreased DLCO is seen in emphysema.
 - In restrictive lung disease decreased DLCO is seen in interstitial lung disease.

II. Obstructive & Restrictive Lung Diseases:

	<u>Obstructive Lung Diseases</u>	<u>Restrictive Lung Diseases</u>
Total lung capacity (TLC)	Increased	Decreased
Residual volume (RV)	Increased	Decreased
FEV ₁	Decreased	Normal or decreased
FEV ₁ /FVC	Decreased	Increased
Peak expiratory flow (PEF)	Decreased	Normal

Obstructive Lung Diseases

Asthma:

I. Introduction:

- It is chronic inflammatory **reversible disorder** with airway hyper-reactivity (AHR) and variable airflow obstruction.
- AHR is the tendency for airways to narrow excessively in response to triggers that have little-to-no effect in normal individuals.
- **Clinical Features:**
 - Classical triad of “**wheezing**”, “**breathlessness**”, and “**cough**”, and chest tightness
 - Episodes have “**diurnal pattern**” – symptoms & lung function are worse in EARLY MORNING.
 - Wheezing (during inspiration and expiration) – most common finding on examination.
 - Exacerbations are associated with:
 - Tachypnea, tachycardia
 - Use of accessory muscles of respiration
 - Diaphoresis (sweating), Fatigue
 - Pulsus paradoxicus
- **Triggers (precipitants):**
 - Respiratory irritants (e.g. smoke, perfume)
 - Allergens (e.g. pets, dust, mites, pollens)
 - Infection (e.g. upper respiratory infection, sinusitis)
 - Drugs (aspirin, NSAIDs, beta blockers)
 - Emotional stress
 - Exercise
 - Cold temperature and air pollutants

Clinical Pearl:

“Asthma Plus” Syndromes:

- **Atopy** = asthma + allergic rhinitis + atopic dermatitis
- **Churg-Strauss Syndrome** = asthma + eosinophilia + granulomatous vasculitis
- **Aspirin-sensitive Asthma (Samter’s syndrome)** = asthma + aspirin sensitivity + nasal polyps
- **Allergic bronchopulmonary aspergillosis** = asthma + pulmonary infiltrates + allergic reaction to Aspergillus.

II. Diagnosis:

- Obstructive pattern (see PFTs above)
- Diagnostic Criteria:
 - Increase in FEV₁ of $\geq 15\%$ (& 200 ml) with use of a bronchodilator (albuterol).
 - Decrease in FEV₁ of $\geq 15\%$ after 6 minutes of exercise
 - $> 20\%$ peak expiratory flow (PEF) diurnal variation on ≥ 3 days in a week for 2 week.
- Methacholine-Challenge Test:
 - Methacholine is a bronchoconstrictor.
 - Methacholine challenge test differentiates between asthma and COPD.
 - In asthma the test is positive i.e. decreased FEV₁ $\geq 20\%$.
 - In COPD the test is negative i.e. no decrease in FEV₁.
- Other Tests:
 - CBC - eosinophilia
 - Skin testing - identifies specific allergens that provoke bronchoconstriction
 - IgE levels - increased levels in allergic etiology as well as Allergic Bronchopulmonary Aspergillosis (ABPA)

IV.**R_x****Treatment:**▪ **Principles of Management:**

- Patient education & avoidance of triggers (allergens) for all patients.
- Yearly influenza vaccine
- "Step-up" treatment as needed to gain control.
- "Step-down" treatment as tolerated.
- Goal of therapy is to achieve "complete control" i.e.:
 - Daily symptoms ≤ 2 times/week
 - No nocturnal symptoms
 - No limitation of activity
 - Reliever medications ≤ 2 times/week
 - Normal PEF & FEV₁

Clinical Pearl:**"Reliever" Medications:**

- These medications are used as per need for quick symptomatic relief.
 - Short-acting inhaled beta-agonists – albuterol
 - Short-acting inhaled anti-cholinergic – ipratropium

▪ **Step 1 – Mild Intermittent Asthma:**

- **Inhaled Short-Acting Beta Agonists (SABA) – treatment of choice**
SABA = albuterol, terbutaline

- It is indicated in those with mild intermittent asthma i.e.:

- Symptoms less than once a week for 3 months
- <2 nocturnal symptoms/ month

▪ **Step 2 – Regular Preventive Therapy:**

- SABA (as needed), PLUS any one of the following

- **Inhaled low-dose corticosteroids (ICS) – preferred choice**

(ICS = beclomethasone at 200 – 800 µg/day)

- Leukotriene receptor antagonists (LTA) – montelukast, zafirlukast
- Mast cell stabilizers -- cromolyn sodium, nedocromil

- Indications:

- Exacerbation of asthma in the last 2 years
- Use of inhaled beta agonist ≥ 3 times/week
- Symptoms ≥ 3 times/week
- Awakened by asthma one night/week.

▪ **Step 3 – Add-On Therapy:**

- SABA (as needed), PLUS any one of the following:

- **Low-dose ICS + long-acting beta agonist (LABA) – preferred choice**

(LABA = salmeterol, formoterol)

- Low-dose ICS + long-acting anti-cholinergics (LAA) – tiotropium
- Increase the dose of ICS
- Low-dose ICS + leukotriene antagonists (LTA) – montelukast
- Low-dose ICS + theophylline



Clinical Pearl:

Long-Acting Beta Agonists (LABA):

- LABA increase PEF when added to ICS.
- LABA should always be combined with ICS (except for exercise-induced asthma).
- LABA monotherapy (without ICS) is associated with:
 - Poor compliance & increased risk of exacerbations.
 - Increased mortality (esp. in blacks)

▪ **Step 4 – Persistent Poor Control:**

- SABA (as needed), PLUS ≥ 1 of the following options:
 - Maximum dose of ICS (up to 2000 $\mu\text{g/day}$) + LABA
 - Maximum dose of ICS + LAA
 - Add a 4th drug:
 - Add oral leukotriene antagonists (LTA) – OR
 - Add oral theophylline

▪ **Step 5 – Severe Asthma:**

- Step – 4 Medications, PLUS any one of the following:
 - Oral Steroids – preferred option
 - Anti-IgE therapy –not cost effective
- Oral steroids should be given in lowest possible dose providing adequate control.
- “Omalizumab” is a monoclonal anti-IgE antibody.
- Indication is severe asthma i.e.:
 - Daily symptoms with frequent nocturnal symptoms.
 - Frequent emergency room admissions and hospitalizations.
 - FEV1 < 60%.
- Side-Effects:
 - Risk of steroid side-effects is increased in patients:
 - On long-term therapy (> 3 months) – OR
 - > 3 – 4 courses per year

V. Acute Asthma Exacerbation:

- It is characterized by increased symptoms, deterioration of lung function, and increased airway inflammation.
- **Triggers of Exacerbations:**
 - Viral infection (most common)
 - Moulds (Alternaria, Cladosporium)
 - Pollen
 - Air pollution
- **Features:**
 - Life-threatening Features:
 - Peak expiratory flow (PEF) <33% predicted (< 100 L/min)
 - $\text{SaO}_2 < 92\%$ or $\text{PaO}_2 < 60 \text{ mmHg}$.
 - Normal (increased) PaCO_2 :
 - **Acute asthmatics have tachypnea, which should decrease PaCO_2 .**
 - **Normal or increased PaCO_2 suggests respiratory muscle fatigue & impending respiratory failure**
 - Silent chest (absence of wheezes) – because of no air movement
 - Feeble respiratory effort
 - Bradycardia or arrhythmia
 - Cyanosis
 - Hypotension
 - Confusion & coma

Severity of Asthma Exacerbations

Breathlessness	With walking	With talking	At rest
Talking	In sentences	In phrases	In words
Mental status	Agitated	Agitated	Agitated
Resp. Rate	Increased	Increased	> 30
Heart Rate	< 100	100 – 120	> 120
Accessory Muscles	No	Yes	Yes
Wheeze	Moderate (end-expiratory)	Loud	Loud
Pulsus paradoxicus	Normal (< 10)	10 – 25	> 25
PEF	> 80%	80 – 60%	< 60%
SaO_2	> 95%	91 – 95%	≤ 90%
PaO_2	Normal	> 60	< 60
PaCO_2	< 45%	< 45%	> 45%

▪ **Investigations:**

○ PEF:

- It should be measured in all patients & is used to follow the clinical course.
- It should be recorded every 15 – 30 minutes, then every 4 – 6 hours

○ ABGs:

- It should be measured in all patients.
- PaCO₂ is initially low (normal – high levels suggest muscle fatigue)



Management:

- "Oxygen" – High concentration (& humidified) to keep SaO₂ > 92%
- "Bronchodilator":
 - Short acting beta-agonists (SABA) are first line agents.
 - Route:
 - Metered-dose Inhaler (MDI) 4 – 8 puffs – OR
 - Via nebulizer 2.5 – 5 mg every 20 minutes.
- "Systemic Steroids" – PO (0.5 – 1 mg/kg) or IV if impending respiratory failure
- Severe Asthma:
 - "Ipratropium" – MDI (4 – 8 puffs) or Nebulizer 0.5 mg every 20 minutes
 - "IV magnesium" – provides bronchodilation (in those with PEF < 30%).
- "Endotracheal Intubation":

(Managed in ICU):

 - Coma
 - Confusion, exhaustion, drowsiness
 - Respiratory arrest
 - Arterial Blood Gases (ABGs) deterioration:
 - PaO₂ < 60 mmHg and falling
 - PaCO₂ > 45 mmHg and rising
 - pH low and falling (acidosis)

○ **Disposition:**

- Decide disposition within 4 hours of presentation & after 1–3 hours of treatment.
- Good Response:
 - PEF ≥ 70%, SaO₂ > 90%, normal exam, no symptoms
 - Response maintained 60 minutes after treatment

- Can be discharged home.
- Incomplete Response:
 - PEF 40 – 69%, mild-to-moderate signs & symptoms
 - Consider admission to hospital ward
- Poor Response:
 - PEF < 40, PaO₂ < 60, PaCO₂ > 42, severe symptoms, altered mental status
 - Admit to ICU.

Chronic Obstructive Pulmonary Disease (COPD):

I. Introduction:

- It refers to **irreversible obstruction of the airways** characterized by progressive airflow limitation caused by airway and parenchymal inflammation.
- It is collective term for both emphysema and chronic bronchitis.

▪ Risk Factors:

- Smoking – most important risk factor:
 - It is unusual to develop COPD with < 10 pack years.
 - 1 pack year = 20 cigarettes per day per year.
- α_1 -antitrypsin deficiency
- Occupation (coal miners, cadmium exposure)
- Chronic asthma
- Cannabis smoking

▪ Types:

(i). Emphysema:

- It refers to permanent enlargement of the air spaces distal of the terminal bronchiole, accompanied by destruction of their walls.
- Centriacinar Emphysema:
 - It is the most common type of emphysema; affects the upper lobes.
 - It occurs in heavy smokers and is associated with chronic bronchitis.
- Panacinar Emphysema:
 - It affects the lower lobes, and is most severe at the bases.
 - It is associated with α_1 -antitrypsin deficiency.

(ii). Chronic Bronchitis:

- It refers to persistent cough with sputum production for at least 3 months in 2 consecutive years.

II. Clinical Features:▪ **Symptoms:**

- Patient over the age of 40 years
- Chronic cough, sputum production
- Dyspnea worsened by exertion
- Intermittent exacerbations – advanced stages
- Weight loss

▪ **Signs:**

- Increased anteroposterior diameter of chest (Barrel-Chest)
- Breath sounds decreased, with hyperresonant percussion note.
- **Increased expiratory phase**, rhonchi, wheezes
- Decreased diaphragmatic excursion
- Weight loss and cachexia
- Headache due to hypercapnia (from carbon dioxide retention)

<u>Pink Puffers</u>	<u>Blue Bloaters</u>
Predominant emphysema	Predominant bronchitis
Thin individuals	Overweight
No cyanosis	Cyanosis (due to hypercapnia & hypoxemia)
Breathlessness, use of accessory muscles	No distress, no use of accessory muscles
Tachypnea with prolonged expiration through pursed lips.	Respiratory is normal or slightly increased.
Normal PaCO ₂	Increased PaCO ₂ (hypercapnia), Secondary polycythemia due to hypoxemia.

III. Diagnosis:▪ **Pulmonary Function Testing:**

- PFTs are the diagnostic test of choice.
- Obstructive pattern (see PFTs above)
- Negative Methacholine challenge test (in contrast to asthma).
- DLCO:
 - Obstructive pattern on PFTs plus decreased DLCO = emphysema
 - Obstructive pattern on PFTs plus negative Methacholine test with normal DLCO = chronic bronchitis
 - Obstructive pattern on PFTs plus positive Methacholine test with normal DLCO = asthma

▪ **Lab Findings:**

- CBC = increased hematocrit (secondary polycythemia from tissue hypoxia)
- ECG = right atrial hypertrophy and right ventricular hypertrophy
- CXR:
 - Hyper-inflated lungs
 - Flattened diaphragm
 - Small tubular heart
 - Increased anteroposterior diameter

IV.

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Management:

- Yearly influenza vaccine
- 5-yearly pneumococcal vaccine
- **Improves Mortality:**
 - **Smoking cessation – is the most important intervention**
 - **Long-term oxygen therapy (LTOT):**
 - It should be used for minimum of 15 hours per day.
 - It provides more benefit if used > 20 hours per day.
 - Indications are:
 - $\text{PaO}_2 \leq 55 \text{ mmHg}$
 - $\text{SaO}_2 \leq 88\%$
 - Ideal target:
 - $\text{PaO}_2 > 60 \text{ mmHg}$
 - $\text{SaO}_2 > 90\%$

▪ **Symptomatic Treatment (doesn't improve survival):**

- **Bronchodilators:**
 - These are the first-line therapy.
 - Anti-cholinergic agents: short acting (ipratropium) long-acting (tiotropium)
 - Short acting beta agonists (SABA)
 - Long acting beta agonists (LABA)
 - Long-acting Anticholinergic (LAA) – Tiotropium:
 - It decreases exacerbations, hospital admissions, and respiratory failure
 - It is better than ipratropium or LABA as monotherapy.

- **Inhaled steroids:**
 - ICS reduce the frequency & severity of exacerbations.
 - It is more effective when combined with LABA.
 - Indications:
 - Severe disease ($FEV1 < 50\%$)
 - Patients with ≥ 2 exacerbations/year requiring antibiotics or oral steroids
- **Antibiotics:**
 - Daily azithromycin decreases exacerbations.
 - However, it is not yet routinely recommended.
- Pulmonary rehabilitation
- Surgery – lung transplant
- **Prognosis:**
 - Prognosis is inversely related to age.
 - Prognosis is directly related to FEV1 i.e. the higher the FEV1, the better the survival

V. Acute Exacerbations of COPD:

- It is characterized by an increase in symptoms & deterioration in lung function and health status.
- Physical Examination:
 - Tachypnea, Accessory muscle use
 - Pulsus paradoxicus, Cyanosis



Treatment:

- **"Oxygen":**
 - 24 – 28% oxygen should be used.
 - High concentration O_2 should be avoided, (causes respiratory depression & acidosis)
 - Targets:
 - $PaO_2 > 60$ mmHg
 - SaO_2 between 88% - 92%
- Bronchodilators:
 - **"Anti-cholinergic agent"** (ipratropium) – first-line agents, PLUS:
 - **"Short-acting beta agonist"** (albuterol)

- **“Steroids”:**
 - Oral steroids (prednisolone 30 mg/day x 10 days)
 - IV steroids (methylprednisolone 125 mg IV 6 hourly x 72 hours) – severe cases
- **“Antibiotics”:**
 - Amoxicillin
 - Macrolides (azithromycin, clarithromycin)
 - Cephalosporins (cefuroxime, cefixime)
 - Quinolones (levofloxacin, moxifloxacin)
 - **No single antibiotic is proven to be superior to others.**
- **“Non-invasive ventilation (NIV)”:**
 - Initiate early in patients with moderate-to-severe dyspnea.
 - It is not useful in patients who cannot protect their airway.
 - If initiated early, it reduces:
 - The need for endotracheal intubation
 - Treatment failure, and mortality.
 - Indications:
 - Persistent tachypnea
 - Respiratory acidosis ($\text{pH} < 7.35$) ($\text{PaCO}_2 > 45$ mmHg)

Bronchiectasis:

I. Introduction:

- **“Definition”:** It refers to obstructive airway disease of bronchi and bronchioles, characterized by:
 - Chronic transmural inflammation, with airway dilatation, thickening, collapsibility, and
 - Mucus plugging with impaired clearance.
- **Causes:**
 - **Congenital Causes:**
 - Cystic fibrosis – most common cause in US
 - Primary Ciliary Dyskinesia:
 - It is also known as **“Immotile Cilia Syndrome”**.
 - It is autosomal recessive.
 - It is characterized by absent or short dynein arms resulting in immotile cilia.
 - In males this condition is associated with infertility.

- **"Kartagener Syndrome":**

- It is present in half of patients with primary ciliary dyskinesia.
- It is characterized by bronchiectasis, sinusitis, and situs inversus.

- **Acquired Causes:**

- Autoimmune disease – rheumatoid arthritis, SLE
- Chronic Infections:
 - Tuberculosis – most common cause worldwide
 - Allergic bronchopulmonary aspergillosis (ABPA)
 - Suppurative pneumonia
 - Airway obstruction (bronchial tumors)

II. Clinical Findings:

- **Chronic cough with copious foul-smelling sputum**
- **Hemoptysis** – due to rupture of blood vessels near bronchial wall surfaces
- Dyspnea
- Recurrent pneumonia
- Coarse crackles over the affected areas.
- Associated with:
 - Fever
 - Weight loss, anorexia
 - Digital clubbing
 - Halitosis
- **Complications:**
 - Cor Pulmonale
 - Respiratory failure
 - Metastatic brain abscess
 - Amyloidosis

III.

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Management:

- **Helical CT scan – investigation of choice**
- PFTs – obstructive pattern (table above)
- Chest X-ray – “**Tram-Tracking**” i.e. cystic shadows and thickened bronchial walls.
- Treatment:
 - Bronchial Hygiene:
 - Hydration
 - Chest physiotherapy (postural drainage, chest percussion) – helps remove the mucus
 - Antibiotics:
 - Antibiotics are given for superimposed infections
 - Antibiotic options are exactly the same as for COPD exacerbation
 - Steroids (for ABPA)
 - Surgery – excision of bronchiectatic areas.

IV. Cystic Fibrosis (CF):

- It is the most common fatal genetic disease in Caucasians.
- Pathogenesis:
 - Inheritance = autosomal recessive
 - Mutations = affecting gene on the long arm of chromosome 7, which codes for chloride channel known as “cystic fibrosis transmembrane conductance regulator” (CFTR) that influences salt & water movement across epithelial cell membranes.
 - The genetic defect causes increased sodium chloride content in sweat and increased resorption of sodium and water from respiratory epithelium.
- Clinical Features:
 - Recurrent pneumonia (initially with staphylococcus aureus, then with pseudomonas)
 - Recurrent bronchiectasis
 - Men are infertile (due to absence of vas deferens)
 - Complication:
 - Respiratory:
 - Pneumothorax; Nasal polyps
 - Hemoptysis; Respiratory failure
 - Gastrointestinal:
 - Malabsorption and steatorrhea; Intestinal obstruction

- Biliary cirrhosis and portal HTN; Gallstones
- Others:
 - Diabetes (25% of adults)
 - Osteoporosis

▪ **Diagnosis:**

- Sweat test = sweat sodium and chloride > 60 mmol/L,
- Genetic testing for CF mutations

▪ **Management:**

- Pancreatic enzyme replacement; fat-soluble vitamin replacement
- Chest physiotherapy
- Vaccinations (influenza and pneumococcal)
- Antibiotics for infections
- Inhale recombinant human deoxyribonuclease (rhDNase), which breaks down DNA in respiratory mucus that clogs the airways.

Restrictive Lung Diseases

I. Diffuse Parenchymal Lung Disease (DPLD):

- This is a group of heterogeneous conditions affecting the pulmonary interstitium and alveolar lumen.
- These conditions differ from each other on the basis of their natural history but they share similar symptoms, physical signs, pulmonary function abnormalities and radiologic changes.
- **Classification of DPLD:**
 - **Idiopathic Interstitial Pneumonias:**
 - Idiopathic Pulmonary Fibrosis (IPF)
 - Cryptogenic Organizing Pneumonia (COP)
 - Lymphocytic Interstitial Pneumonia
 - Non-specific Interstitial Pneumonia
 - Acute Interstitial Pneumonia
 - Respiratory bronchiolitis interstitial lung disease (RBILD)
 - **Granulomatous DPLD:**
 - Sarcoidosis
 - Histiocytosis X
 - Wegener's granulomatosis
 - Churg – Strauss syndrome
 - **DPLD associated with Connective Tissue Disease:**
 - Rheumatoid Arthritis, Scleroderma
 - SLE, Mixed Connective Tissue Disease
 - **Environmental Lung Disease:**
 - Coal worker's pneumoconiosis
 - Silicosis, Asbestosis, Berylliosis
 - **Hypersensitivity Lung Disease:**
 - Hypersensitivity pneumonitis
 - Eosinophilic pneumonitis

II. Idiopathic Pulmonary Fibrosis (IPF):

(i). Introduction:

- It is the most common type of idiopathic interstitial pneumonia.
- **Definition:** progressive fibrosing interstitial pneumonia of unknown cause, associated with radiologic and histologic pattern called "Usual Interstitial Pneumonia" (UIP).

▪ **Clinical Features:**

- 50 – 70 years of age (uncommon before 50 years).
- **Progressive dyspnea and a non-productive (dry) cough.**
- **Hypoxemia and finger clubbing.**
- **Bi-basal fine end-inspiratory crepitations (crackles)**
- Central cyanosis and right heart failure in advanced cases.

(ii).

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Management:

▪ **Investigations:**

- PFTs show restrictive pattern.
- CXR:
 - Initially = ground-glass appearance
 - Followed by = irregular reticulonodular shadowing (mainly in lower lobes)
 - Eventually = honeycomb lung.
- High-resolution CT scan (HRCT):
 - **It is the critical first step in the investigation of DPLD.**
 - It shows findings similar to CXR, but is more sensitive.
- Lung biopsy:
 - Transbronchial lung biopsy
 - Video-assisted thoracoscopic lung biopsy

▪ **Treatment:**

- Treatment is difficult.
- Supportive Therapy:
 - Oxygen – for dyspnea
 - Opiates – for severe dyspnea
 - Thalidomide – for cough
 - Steroids – (prednisolone 0.5 mg/kg)
 - Immunosuppressant – (azathioprine)
 - Tyrosine kinase inhibitor – (nintedanib)
 - Anti-fibrotic agents – (pirfenidone)
 - Definitive therapy – lung transplantation

III. Sarcoidosis:

(i). Introduction:

- It is a chronic multisystem disease of unknown etiology characterized by “**non-caseating granulomas**”.
- **Clinical Features:**
 - It affects females > males.
 - It typically occurs in African-American population.
 - It presents between 20 – 40 years of age.
 - Constitutional Symptoms:
 - Fever, malaise, fatigue, and weight loss
 - These can be absent in many patients.
 - Lungs:
 - Most common site (90%)
 - Dry cough, dyspnea on exertion
 - Occasional fine rales on examination (without wheezing)
 - Bilateral hilar lymphadenopathy (BHL).
 - Skin:
 - Skin is the most common extra-pulmonary presentations.
 - Erythema Nodosum; nasal cutaneous sarcoid (“**lupus pernio**”).
 - CNS = “**facial nerve palsy**”, space-occupying lesion, peripheral neuropathy
 - CVS = cardiac arrhythmia; heart block, sudden death
 - Hepatobiliary = granulomatous liver disease; splenomegaly
 - Kidneys = Nephrocalcinosis; Renal stones
 - Eyes = “**anterior uveitis**” > posterior uveitis; sicca syndrome
 - Glands = lacrimal gland enlargement; “**parotid gland enlargement**”

Clinical Pearl:

Sarcoidosis:

- “**Erythema Nodosum**”:
 - These are painful purplish nodules usually occurring over the shins.
 - They regress spontaneously, leaving a bruised appearance.
- “**Lofgren Syndrome**”:
 - Association of erythema nodosum + arthritis + hilar adenopathy.
 - It carries good prognosis.
- “**Heerfordt Syndrome**”:
 - Association of fever + facial nerve palsy + parotid enlargement + uveitis.

(ii). Diagnosis:**▪ Lab Findings:**

- Serum angiotensin converting enzyme (ACE) Levels:
 - It is elevated in 50 – 60% of cases – a non-specific marker of disease activity.
 - It can assist in monitoring of disease activity.
- Hypercalcemia – due to formation of Vitamin D by alveolar macrophages.
- Hypercalciuria
- Increased ESR
- Increased immunoglobulins
- **Lymphopenia – characteristic finding**
- PFTs – restrictive pattern
- Deranged liver function tests (LFTs)
- Bronchoalveolar Lavage (BAL):
 - Increased lymphocytes in active disease.
 - **Increased CD4: CD8 ratio**
- Biopsy:
 - It is the most accurate test – transbronchial biopsy, lymph node biopsy
 - It shows non-caseating granulomas.
- Chest X-ray:
 - **Bilateral Hilar Lymphadenopathy (BHL) is the hallmark of disease.**
 - CXR is used for staging of the disease.

CXR Changes in Sarcoidosis

Stage I	Bilateral hilar lymphadenopathy (BHL)
Stage II	BHL + parenchymal infiltrates
Stage III	Parenchymal infiltrates without BHL.
Stage IV	Pulmonary fibrosis

(iii).

R_x**Management:**▪ **Treatment:**

- Acute disease = bed rest, and NSAIDs
- Indications for corticosteroids (prednisolone 20 – 40 mg/day)
 - Parenchymal lung disease
 - Uveitis
 - Hypercalcemia
 - Neurologic involvement
 - Renal impairment
 - Cardiac involvement

▪ **Poor Prognosis:**

- Age > 40 years
- Afro-Caribbean ethnicity
- Persistent symptoms for > 6 months
- Involvement of > 3 organs
- Lupus pernio
- Stage III or IV chest x-ray

IV. Hypersensitivity Pneumonitis (Organic Dusts):**(i). Introduction:**

- It is also known as “**extrinsic allergic alveolitis**”.
- It results from the inhalation of a wide variety of **organic antigens**.
- It is an immunologic response to an extrinsic antigen that involves both immune complex and delayed hypersensitivity reactions.
- **It is therefore a pneumonitis having both Type-III and Type-IV hypersensitivity reactions.**
- Types:

<u>Disorder</u>	<u>Source</u>	<u>Antigen/Agent</u>
Farmer's Lung	Mouldy hay	Thermophilic actinomycetes bacteria
Bird fancier's lung	Avian excreta, proteins, & feathers	Avian serum proteins
Byssinosis	Textile industries	Cotton, hemp dust
Humidifier (inhalational) fever	Contamination of air conditioning	Thermophilic actinomycetes bacteria
Cheese worker's lung	Mouldy cheese	Aspergillus clavatus

(ii). Clinical findings:▪ **Acute form:**

- It occurs in patients with exposure to high-antigen load.
- It presents with influenza-like symptoms.
- Recurrent episodes of fever, malaise, headache
- Cough, dyspnea, wheeze
- Leukocytosis
- Chest X-ray = ill-defined, patchy airspace shadowing
- HRCT:
 - Bilateral ground-glass appearance (affects upper & middle lobes)
 - Areas of consolidation superimposed on nodular opacities.

▪ **Chronic form:**

- It occurs in patients with exposure to low-antigen load.
- It presents with progressive worsening dyspnea and progressive respiratory failure.
- Auscultation reveals wide-spread end-inspiratory crackles
- CXR = features of pulmonary fibrosis
- PFTs = restrictive pattern
- HRCT = pulmonary fibrosis (volume loss, linear opacities, architectural distortion)

(iii). Treatment:

- **Remove exposure to inciting agent**
- Dusk mask with filters
- Acute Form:
 - Prednisolone for 3 – 4 weeks
 - High-concentration oxygen – severely hypoxemic patients
- Complications:
 - Pulmonary fibrosis ----- Hypoxemia
 - Pulmonary hypertension ----- Cor Pulmonale ----- Death

V. Occupational Lung Diseases (Inorganic Dusts):

- Pneumoconiosis is an occupational lung disease with restrictive pattern, caused by inhalation of dusts (organic & inorganic).

(i). Coal-Workers' Pneumoconiosis (CWP):

- It is pneumoconiosis caused by inhalation of coal dust.
- Occupation – coal mining.
- Types:

○ **Simple Coal Worker's Pneumoconiosis (SCWP):**

- It is characterized by small radiographic nodules in an asymptomatic patient.
- It doesn't impair lung function.
- It rarely progresses, once the exposure has been ceased.

○ **Complicated CWP (CCWP):**

- Also known as "progressive massive fibrosis" (PMF)
- It is characterized by fibrotic opacities with or without necrotic centers.
- It can cause crippling lung disease, "black-lung disease":
 - Productive cough & dyspnea
 - "**Melanoptysis**" – black sputum
- It can progress even if the exposure has been ceased.
- It leads to respiratory & right heart failure in extreme cases.

(ii). Silicosis:

- It is pneumoconiosis caused by inhalation of crystalline silica.
- It is the most common chronic occupational disease in the world.
- It has two forms; crystalline and amorphous, but crystalline form (quartz) is more fibrogenic and more implicated in silicosis.
- Occupations: mining, stone-cutting, glass manufacturing, metal grinding

▪ **Clinical findings:**

- It affects the upper zones of the lung
- It manifests after 10 – 20 years of continuous silica exposure.
- It is usually a progressive disease, even when exposure ceases.
- Early stage – asymptomatic
- Advanced stages – dyspnea, cough
- Radiologic Appearance:
 - **Nodular opacities (3-5 mm) in the mid- and upper zones.**
 - "**Egg-shell**" calcification in hilar nodes:
 - It refers to rim of dystrophic calcification in hilar nodes.
 - It is uncommon and non-specific.

▪ **Complications:**

- Increased susceptibility to **tuberculosis** (due decreased cell-mediated immunity)
- Lung cancer
- COPD
- Associated with connective tissue disease

- Associated with renal disease
- Treatment – removal from exposure to silica

(iii). Asbestos-related Diseases:

- It is pneumoconiosis caused by inhalation of asbestos.
- It presents ≥ 20 years after first exposure to the agent.
- Types of Asbestos:
 - Chrysotile (white asbestos) – most common type, but not associated with mesothelioma.
 - Crocidolite (blue asbestos) – associated with mesothelioma.
- Associated Diseases:
 - **Benign pleural plaques:**
 - Most common manifestation of past asbestos exposure
 - These are discrete circumscribed areas of hyaline fibrosis.
 - These are always asymptomatic.
 - Involves “parietal pleura” of chest wall, diaphragm, pericardium, & mediastinum
 - **Diffuse Pleural Thickening:**
 - It affects the “visceral pleura”.
 - It presents with exertional dyspnea, chest pain, and restrictive lung disease.
 - **Asbestosis:**
 - It refers to diffuse parenchymal lung disease.
 - Clinical Features:
 - Exertional dyspnea; productive cough
 - Fine late-inspiratory crackles over the lower zones.
 - Digital clubbing
 - Progressive respiratory failure; Cor Pulmonale
 - Complications:
 - Lung cancer – 40% (risk is increased with concomitant tobacco smoking)
 - Mesothelioma – 10% (not associated with concomitant tobacco smoking)
 - **Mesothelioma:**
 - It refers to malignant tumor of pleura (& less commonly, peritoneum).
 - Its presence invariably suggests past asbestos exposure.

- Clinical Features:
 - Dyspnea (pleural effusion), chest pain
 - Involvement of adjacent structures
- Treatment:
 - It is invariably fatal.
 - Chemotherapy - improves quality of life & survival benefit of 3 months
 - Radiotherapy - controls pain & limits the risk of seeding at biopsy sites
 - Pleural effusion - drainage & pleurodesis

VI. Respiratory Complications of Systemic Diseases:

(i). Rheumatoid Arthritis:

- Manifestations:
 - Pulmonary fibrosis – most common
 - Pulmonary nodules
 - Pleurisy
 - Caplan's Syndrome (rheumatoid nodules + pneumoconiosis)
 - Bronchitis & bronchiectasis
 - Pleural effusion:
 - It is more common in men with seropositive disease.
 - It is usually small and unilateral.
 - It is an exudative effusion with low glucose and raised LDH.

(ii). Systemic Lupus Erythematosus (SLE):

- Lung involvement is more common in SLE than in any other connective tissue disorder.
- Manifestations:
 - Venous & Pulmonary Thromboembolism:
 - It is common in SLE patients with anti-phospholipid antibodies.
 - It requires life-long anticoagulation.
 - Pleurisy
 - Pulmonary fibrosis
 - Acute Alveolitis:
 - It is the most serious manifestation of lupus.
 - It is associated with diffuse alveolar hemorrhage.
 - It is a life-threatening condition requiring immunosuppression.
 - Shrinking Lungs:
 - It is due to diaphragmatic weakness.

- It is characterized by diaphragmatic elevation on CXR with reduced lung volumes

(iii). Systemic Sclerosis:

- Manifestations:
 - Pulmonary fibrosis – most common
 - Recurrent aspiration pneumonia
 - Bronchiectasis
 - **Hidebound Chest** i.e. sclerosis of skin of chest wall restricts chest wall movement.

Pulmonary Infections

Tuberculosis (TB):

I. Introduction:

- It is the world's leading cause of death from a single infectious disease.
- It is most commonly caused by *Mycobacterium tuberculosis*.
- *Mycobacteria* are acid-fast bacilli (AFB).
- Mode of transmission = inhalation of aerosolized droplet nuclei from infected patients.
- **Pathogenesis:**
 - Bacilli are inhaled and lodge in the alveoli.
 - Bacilli then initiate recruitment of macrophages and lymphocytes.
 - Surviving organisms multiply and disseminate via lymphatics and the bloodstream.
 - Macrophages undergo transformation into Epithelioid and Langerhans cells which aggregate with lymphocytes to form granulomas.
 - "Ghon Focus":
 - It is the primary lesion characterized by aggregation of numerous granulomas in the periphery of lung.
 - "Ghon Complex":
 - It refers to combination calcified primary lesion (i.e. Ghon Focus) with lymph node involvement.
 - "Ranke's Complex":
 - It is formed when Ghon complex undergoes fibrosis and calcification.
 - Reparative processes encase the primary complex in a fibrous capsule limiting the spread of bacilli.
 - After resolution of the primary infection, the organism remains dormant within the granuloma.
 - An insult to the immune system may activate the TB at any time.

II. Features of Pulmonary Disease:

- **Primary pulmonary TB:**
 - It refers to infection of a previously un-infected individual.
 - It is usually asymptomatic.
 - If the immune response is incomplete, the pulmonary and constitutional symptoms of TB may develop, known as "**progressive primary TB**":
 - Influenza-like illness

- Lymphadenopathy
- Collapse of lung (most commonly right middle lobe)
- Consolidation (most commonly right middle lobe)
- Cavitation
- Miliary TB
- Meningitis
- Pericarditis

▪ **Secondary (Active) TB:**

- Also known as “post-primary TB”.
- It occurs when the host’s immunity is weakened (e.g. HIV, malignancy, DM)
- Clinical Features:
 - Affects most oxygenated parts of lungs – apex of upper lobe.
 - Chronic cough, often with hemoptysis
 - Low-grade fever, night sweats, weight loss, and malaise and loss of appetite.
 - Spontaneous pneumothorax
 - Indication of active disease:
 - **Presence of miliary pattern**
 - **Cavitation**

▪ **Miliary TB:**

- It refers to acute diffuse dissemination of tubercle bacilli via bloodstream (Hematogenous).
- Clinical Features:
 - 2-3 weeks of fever, night sweats, anorexia, weight loss and dry cough.
 - Hepatosplenomegaly
 - Headache – may indicate a co-existing meningitis
 - **Fundoscopy = choroidal tubercles**
 - CXR:
 - **“Millet – Seed” appearance** i.e.
 - Fine 1 – 2 mm lesions distributed throughout the lung fields.

▪ **Complications of Pulmonary TB:**

- Massive hemoptysis
- Cor pulmonale
- Aspergilloma
- Bronchiectasis

- Bronchopleural fistula
- Non-pulmonary:
 - Enteritis (from swallowed sputum)
 - Anorectal disease (from swallowed sputum)
 - Poncet's polyarthritis

III. Features of Extra-pulmonary Disease:

▪ Lymph nodes:

- **Lymph nodes are the most common extra-pulmonary site of disease.**
- Most common site = cervical and mediastinal nodes.
- Clinical Features:
 - Painless lymphadenopathy
 - Initially the nodes are mobile.
 - Later the nodes become matted and can suppurate with sinus formation.
 - The tuberculin test is usually strongly positive.
 - **"Scrofula"** refers to massive cervical lymph node enlargement with discharging sinuses.

▪ Gastrointestinal Disease:

- **Most common site = ileocecal region.**
- Main differential diagnosis is Crohn's disease.
- Clinical Features:
 - Fever, night sweats, anorexia, and weight loss.
 - Right iliac fossa mass.
 - Acute abdomen – 30% cases.
 - Tuberculous peritonitis:
 - Abdominal distention, pain and constitutional symptoms.
 - Ascitic fluid is exudative with predominance of lymphocytes.

▪ Pericardial Disease:

- Pericardial Effusion:
 - Breathlessness and abdominal swelling.
 - Fever and night sweats are uncommon.
 - Raised JVP, hepatomegaly, prominent ascites, and peripheral edema.
 - **Increased pericardial dullness & a globular enlarged heart on CXR.**

- Constrictive Pericarditis:
 - Breathlessness and abdominal swelling.
 - Fever and night sweats are uncommon.
 - Raised JVP, hepatomegaly, prominent ascites, and peripheral edema.
 - **Early third heart sound and pericardial calcification in 25% cases.**
- **Central Nervous System:**
 - Meningitis
 - Tuberculoma (a space occupying lesion)
- **Bone & Joint Disease:**
 - Bone:
 - Most common site = spine, known as **Pott's disease**.
 - Most common site of spine = lower thoracic and lumbar region.
 - Clinical Features:
 - Chronic back pain (infection starts as discitis)
 - Kyphosis (involvement of anterior vertebral bodies)
 - **Psoas abscess** – presenting as a cold abscess in inguinal region
 - Main differential diagnosis is malignancy.
 - Malignancy affects vertebral body but leaves the disc intact (i.e. no discitis)
 - Joints:
 - Most common site = hip and knee
 - **Poncet's arthropathy:**
 - It refers to immunologically mediated polyarthritis.
 - It starts within 2 months of starting treatment for TB.

IV. Diagnosis:

- Chest X-ray:
 - Classic findings are upper lobe infiltrates with cavitations.
 - Collapse, calcification, pleural effusion may be present.
- Sputum Staining:
 - Sputum staining (direct microscopy of sputum) is the most important first step.
 - **Positive smear is sufficient for presumptive diagnosis of TB.**
 - Methods:
 - Auramine – Fluorescence Test (sensitive, but complex and expensive)
 - Ziehl – Neelsen Stain (less sensitive.

- If patient is not expectorating (i.e. not producing sputum), then sputum can be obtained:
 - By induction with nebulized hypertonic saline
 - Bronchoscopy and lavage
- Sputum Culture:
 - **Sputum culture is required for definitive diagnosis of TB.**
 - Obtain 3 morning sputum specimens.
 - Methods:
 - Solid media (Lowenstein-Jensen Medium) = takes 4 – 6 weeks
 - Liquid media (BACTEC system) = takes 1 – 3 weeks
 - Nuclide acid amplification (PCR) = more rapidly
- Tests for Extra-pulmonary TB:
 - Fluid Examination (e.g. CSF, ascitic, pleural, joint)
 - Tissue biopsy
 - Bone marrow biopsy
 - Liver biopsy

V.

RX

Management:

(i). Treatment Regimen:

- Initial Phase (2 – months):
 - Four drugs are used (mnemonic: RIPE)
 - Isoniazid
 - Rifampicin
 - Pyrazinamide
 - Ethambutol
- Continuation Phase (4 – months):
 - Two drugs are used:
 - Isoniazid
 - Rifampicin
- Extended Treatment (9 – 12 months):
 - HIV – positive patients
 - Tuberculous osteomyelitis
 - Miliary tuberculosis
 - Meningitis – (minimum 12 months)
 - Pregnancy (because first-line agent pyrazinamide is contraindicated)
 - If drug intolerance occurs and a “second-line agent” is substituted.

**Clinical Pearl:****Isoniazid & Vitamin B6:**

- Isoniazid should always be started with vitamin B6 (pyridoxine) to prevent symptoms of deficiency:
 - Peripheral neuropathy
 - Stomatitis, glossitis, cheilosis, convulsions

Directly Observed Therapy (DOT):

- It involves supervised administration of ATT 3 times per week.
- It aims to improve adherence, which is a major factor in prolonged illness, risk of relapse, and the emergence of drug resistance.

(ii). Drug Dosage:

<u>Drugs</u>	<u>Dose</u>	<u>DOTS (if given 3 times/week)</u>
Isoniazid	5 mg/kg	15 mg/kg
Rifampicin	10 mg/kg	10 mg/kg
Ethambutol	15 – 25 mg/kg	25 – 30 mg/kg
Pyrazinamide	15 – 30 mg/kg	50 – 70 mg/kg
Streptomycin	15 mg/kg	25 – 30 mg/kg
DOTS = directly observed therapy short-course		

(iii). Drug Complications:

<u>Drug</u>	<u>Toxicity</u>	<u>Management</u>
Isoniazid	Hepatitis; Peripheral neuropathy SLE-like syndrome; Psychosis	Pyridoxine (Vit.B6)
Rifampicin	Orange – red color to body secretions (urine, tears) Hepatitis; thrombocytopenia	Orange coloration is a benign finding; doesn't need treatment.
Ethambutol	Optic neuritis (color blindness for green, decreased visual acuity, central scotoma)	Reduce the dose, or stop.
Pyrazinamide	Hepatitis, photosensitization, hyperuricemia, gout.	Contraindicated in pregnancy
Streptomycin	8 th (vestibular) nerve damage. Agranulocytosis, nephrotoxicity	It is used only if patient has multi-drug resistant TB, or not responding to therapy.

(iv). Second-line Drugs:

- Quinolones (e.g. ofloxacin)
- Amikacin
- Kanamycin; Capteomycin
- Cycloserine



Clinical Pearl:

I. Role of Steroids:

- Corticosteroids are indicated in tuberculosis in following conditions:
 1. Pericardial disease (decreases the risk of constrictive pericarditis)
 2. Tuberculous meningitis (decreases the risk of neurologic complications)

II. Multi-Drug Resistant TB (MDR-TB)

- WHO definition = drug resistance to isoniazid and rifampicin.

III. Extensive-Drug Resistant TB (XDR-TB)

- WHO definition = drug resistance to isoniazid, rifampicin, quinolone and at least ONE of the following 2nd – line drugs:
 - Kanamycin
 - Capteomycin
 - Amikacin

VI. PPD Testing (Mantoux test) & Treatment:

- PPD skin testing is not a general screening test for the whole population.
- PPD skin testing is useful in those with risk factors mentioned below.
- **PPD is indicated in those with latent TB (asymptomatic patients)**
- PPD is NOT useful in those who are symptomatic or those with abnormal CXR; these patients should have sputum acid fast testing rather than PPD.
- **Mechanism:**
 - It is based on cell-mediated immunity with development of induration and inflammation at the site of infection due to infiltration with mainly T-lymphocytes.
 - Method:
 - Intra-dermal (volar aspect of forearm) injection of 0.1 mL of a 1: 1000 strength PPD.
 - Induration (not erythema) is measured after 72 hours.
- **Positive Test:**
 - Induration of > 15 mm is considered positive in those with no risk factors.
 - Induration of > 10 mm is considered positive in:

- Prisoners
- Healthcare workers
- Close contacts of someone with TB
- Hematologic malignancy
- Alcoholics and diabetes mellitus
- Intravenous drug users
- Induration of > 5 mm is considered positive in:
 - HIV-positive patients
 - Immunocompromised patients (e.g. prednisolone 15 mg/d for > 1 month)
 - Close contact with patients with ACTIVE disease.
 - Abnormal CXR (e.g. apical calcifications)
 - Organ transplant recipients
- False-Negative result:
 - Severe TB (25% cases)
 - Newborn and elderly
 - HIV if CD4 count is < 200 cell/mL
 - Malnutrition
 - Malignancy
- **Guidelines:**
 - If a patient has positive PPD, a second test is not necessary.
 - If a patient has negative PPD now, but has never had PPD skin test before = a second test is indicated within 1 – 2 weeks.
 - If the second test is negative, it means the patient is truly negative.
 - If the second test is positive, it means that the first test was false-negative.
 - Positive PPD test:
 - The first step after a positive PPD test is to do a CXR.
 - If CXR is positive = start anti-tuberculous therapy.
 - If CXR is negative:
 - **Start prophylaxis with isoniazid (INH) for 9 months.**
 - **Start prophylaxis with rifampicin x 4 months in INH-resistant cases**



Clinical Pearl:

BCG (Bacillus Calmette-Guerin) Vaccine:

- It is a live attenuated vaccine derived from mycobacterium bovis.
- It is administered by intradermal injection & is highly immunogenic.
- In children it prevents disseminated disease, and TB meningitis.
- In adults its efficacy is unknown.
- It is a very safe vaccine.
- Contraindications:
 - Immunosuppression (e.g. HIV)
 - Pregnancy

Pneumonia:

- Pneumonia is defined as infection of the lung parenchyma.
- Pneumonia is of following types:

I. Community-acquired Pneumonia (CAP):

- It refers to pneumonia occurring in the community or within first 72 hours of hospitalization.

Types:

(i). Typical CAP:

- Agents:
 - Streptococcus pneumoniae (most common)
 - Hemophilus influenzae
 - Staphylococcus aureus
 - Aerobic gram-negative rods (Klebsiella, Enterobacteriaceae)
- Presentation:
 - Sudden onset productive cough (purulent sputum)
 - Dyspnea & pleuritic chest pain
 - Fever, rigors, and chills.
 - Signs:
 - Tachycardia, Tachypnea
 - Bronchial breath sounds, dull percussion note, increased vocal fremitus
- CXR = consolidation

(ii). Atypical CAP:

- Agents:
 - Legionella pneumophila
 - Mycoplasma
 - Chlamydia
 - Pneumocystis carinii
 - Viral
- Presentation:
 - Gradual onset.
 - Dry (non-productive) cough
 - Extra-pulmonary symptoms – headache, myalgias, and GI-symptoms
 - CXR = bilateral interstitial infiltrates (no consolidation)

**Clinical Pearl:****Atypical Pneumonia:**

- It is pneumonia caused by organisms that are:
 - Not visible on Gram stain
 - Not culturable on standard blood agar

Investigations:

- Chest x-ray
- Blood Tests:
 - Complete blood count – leukocytosis
 - Urea, creatinine, electrolytes (UCE)
 - Blood cultures
 - Liver function tests
 - C-reactive protein
 - Arterial blood gases (ABGs)
- Bronchoalveolar Lavage:
 - If patient is immunocompromised
 - If patient is in ICU.

▪ **Organism-Specific Pneumonias:**

<u>Organism</u>	<u>Features</u>
<u>Streptococcus pneumoniae</u>	Gram positive lancet-shaped diplococcus. Rust color sputum. Most common cause of community-acquired pneumonia. Drug of choice: penicillin G, amoxicillin
<u>Staphylococcus aureus</u>	Gram positive cocci in clusters. Yellow sputum. Most common cause of pneumonia post-influenza. Association = intravenous drug abuse Causes bilateral cavitary bronchopneumonia. Drug of choice for methicillin sensitive S. aureus = flucloxacillin. Drug of choice for methicillin resistant S. aureus (MRSA) = vancomycin
<u>Hemophilus influenzae</u>	Gram negative rod; with polysaccharide capsule Association = COPD, smokers Most common bacterial cause of acute exacerbation of COPD.
<u>Klebsiella pneumoniae</u>	Gram negative rod with a mucoid capsule, " Friedlander's bacillus " Association = elderly patients in nursing homes, alcoholism, diabetes "Currant jelly" sputum (blood tinged, thick, mucoid sputum). Drug of choice = ceftriaxone
<u>Legionella pneumophila</u>	Gram negative rod. Association = water coolers, air-conditioning, ventilation systems. Risk factors = alcoholics, immunocompromised (e.g. organ transplant patients) Pneumonia with GI-symptoms (abdominal pain, diarrhea), CNS-symptoms (headache and confusion), hyponatremia, deranged liver function tests.
<u>Mycoplasma pneumoniae</u>	Bacteria with no cell wall (no visible on Gram stain) Atypical pneumonia, erythema multiform Complications = Stevens-Johnson syndrome, Guillain-Barre syndrome.
<u>Pseudomonas aeruginosa</u>	Gram negative rod; green sputum. Most common cause of nosocomial pneumonia. Most common cause of death due to pneumonia in patients with cystic fibrosis.

▪ **Complications:**

- Para-pneumonic effusion
- Abscess formation
- Empyema (pus in pleural cavity)
- Deep venous thrombosis and pulmonary embolism
- Bacteremic dissemination (sepsis)

▪ **Severity of Pneumonia:**



Clinical Pearl:

CURB-65:

- It is a scoring system for assessing severity of pneumonia.
- Score of 0 – 1 can be managed on outpatient basis.
- Score of 2 is criteria for inpatient management.
- Score of ≥ 3 means severe pneumonia (assess for ICU admission)
 - **C** = Confusion (Mental Test Score of ≤ 8).
 - **U** = Blood urea nitrogen (BUN) > 30 mg/dL.
 - **R** = Respiratory rate > 30 minute
 - **B** = Blood pressure (systolic < 90 , or diastolic < 60)
 - **65** = Age > 65 years

Other Markers of Severity:

1. CXR – more than one lobe involved.
2. $\text{PaO}_2 < 60$ mmHg
3. Low albumin < 35 g/L
4. $\text{WBC} < 4 \times 10^9/\text{L}$ OR $> 20 \times 10^9/\text{L}$
5. Blood culture positive.

R
X**Treatment:**

- The most important aspect of treatment is to decide whether to hospitalize the patient or treat as an outpatient.
- This decision is made not only on the basis of severity scores (e.g. CURB-65), but clinical judgement is also critical.
- Duration of Treatment:
 - CAP – 5-7 days, do NOT STOP treatment until:
 - Clinical improvement, AND
 - Patient is afebrile for 48 – 72 hours
 - HAP:
 - 8 days
 - 15 days if infection with pseudomonas & other non-fermenting gram-negative rods.

○ **Outpatient Treatment:**

Option 1:

- Patients < 60 years of age – OR
- Previously healthy patient – OR
- No antibiotic in the past 3 months
- Treatment:
 - Macrolides – (Azithromycin or Clarithromycin) – OR
 - Doxycycline
 (Organisms covered: *S. pneumoniae*, *Mycoplasma*, *Chlamydia*, *Legionella*)

Option 2:

- Patients > 60 years of age – OR
- Patient with comorbidities – OR
- Antibiotics in the past 3 months
- Treatment:
 - Respiratory fluoroquinolones (Levofloxacin, Moxifloxacin) – OR
 - Macrolide + 2nd or 3rd generation cephalosporin – OR
 - Macrolide + high-dose amoxicillin-clavulanic acid

○ **Inpatient Treatment:**

- Respiratory fluoroquinolones (levofloxacin, moxifloxacin), OR
- Ceftriaxone (3rd-generation cephalosporin) PLUS Azithromycin (macrolide)

II. Hospital – Acquired Pneumonia (HAP):

- Also known as “Nosocomial Pneumonia”.
- It is defined as pneumonia occurring > 72 hours of hospital admission.
- These patients have a higher incidence of gram-negative bacilli infection (E. coli, Pseudomonas).
- Therefore, macrolides are NOT EFFECTIVE empiric therapy in these patients.
- Treatment therefore focuses on gram-negative bacilli.
- Treatment:

(Any ONE of the following agents):

- | | |
|-----------------------------------|---------------------------|
| ○ Anti-pseudomonal Penicillin | - Piperacillin-Tazobactam |
| ○ Anti-pseudomonal Cephalosporins | - Ceftazidime, Cefepime |
| ○ Carbapenems | - Imipenem, Meropenem |

III. Ventilator – Associated Pneumonia (VAP):

- It refers to pneumonia in patients on mechanical ventilation.
- Patients on mechanical ventilation are at risk for developing pneumonia because:
 - Impaired mucociliary clearance of the respiratory tract (cannot cough)
 - Positive pressure impairs the ability to clear colonization

- **Diagnosis:**

- Fever, Rising white cell count
- New infiltrate on CXR
- Purulent secretions from endotracheal tube
- Investigations:
 - Tracheal aspirate
 - Bronchoalveolar lavage (BAL)
 - Video-assisted thoracoscopy – most accurate
 - Open lung biopsy (rarely done)

**Clinical Pearl:****Formula for Treatment of VAP:**

- Select any ONE of following:
 - Anti-pseudomonal penicillin (piperacillin-tazobactam) – OR
 - Anti-pseudomonal cephalosporins (ceftazidime, cefepime) - OR
 - Carbapenems (Imipenem, Meropenem)
- PLUS any ONE of following:
 - Respiratory fluoroquinolone (Levofloxacin, Moxifloxacin) – OR
 - Gentamicin + Azithromycin
- PLUS Methicillin-Resistant Anti-staphylococcal Agent:
 - Vancomycin – OR
 - Linezolid

Fungal Diseases:

I. Allergic Bronchopulmonary Aspergillosis (ABPA):

- It is a hypersensitivity reaction to germinating fungal spores (*Aspergillus fumigatus*).
- **Clinical Features:**
 - Cough, wheezing, hemoptysis
 - **Recurrent episodes of brown-flecked sputum (bronchial casts)**
 - **Worsening of asthmatic patients.**
 - Association:
 - Asthma (1 – 2%)
 - Cystic fibrosis (5 – 10%)
- **Diagnosis:**
 - **CT scan = proximal (inner 2/3rd of chest field) bronchiectasis**
 - Positive skin test to an extract of *A. fumigatus*
 - Elevated total serum IgE levels (> 1000 ng/ml).
 - Eosinophilia
 - Microscopic examination of sputum = fungal hyphae
- **Treatment:**
 - Steroids:
 - Maintenance therapy - low-dose oral steroids (prednisolone 7.5 – 10 mg daily)
 - Acute exacerbation - high-dose steroids (prednisolone 40 – 60 mg)
 - Itraconazole:
 - It is anti-fungal agent (400 mg/day).
 - A 4 – month trial is usually recommended to assess its efficacy.
 - for recurrent episodes

II. Aspergilloma (Fungal Ball):

- It refers to growth of *A. fumigatus* within previously damaged lung tissue where it forms a ball of mycelium within lung cavities.
- **Most common site = upper lobes.**
- **Risk Factors:**
 - **Tuberculous cavities (most common)**
 - Abscess cavity
 - Bronchiectatic space
 - Pulmonary infarct

▪ **Diagnosis:**

- Often asymptomatic
- Recurrent hemoptysis
- CXR:
 - Like carcinoma it produces a tumor-like opacity.
 - Unlike carcinoma it shows "**crescent sign**" i.e. a crescent of air between the fungal ball and upper wall of the cavity.

▪ **Treatment:**

- Asymptomatic patients = no treatment
- Symptomatic patients:
 - Fit for surgery = surgical excision is treatment of choice
 - Unfit for surgery = local instillation of amphotericin B, or bronchial artery embolization.
- Following are NOT useful:
 - Regular antifungal therapy
 - Steroids (may predispose to invasion)

III. Invasive Pulmonary Aspergillosis (IPA):

▪ **Risk Factors:**

- **Neutropenia caused by drugs – most common cause**
- Hematologic malignancy
- Advanced HIV disease
- Severe COPD
- Immunocompromised patients

▪ **Clinical Features:**

- Severe necrotizing pneumonia
- Fever, hemoptysis
- Thrombosis and infarction of pulmonary vessels
- Systemic spread to brain, heart, and kidneys.

▪ **Treatment:**

- **Voriconazole – drug of choice.**
- Alternative agents – Amphotericin B, Caspofungin

Primary Lung Tumors

Benign Tumors:

- Cylindroma
- Chondroma
- Bronchial carcinoid:
 - It produces hemoptysis, cough, and carcinoid syndrome.
 - **Carcinoid syndrome doesn't require liver metastasis.**
- Pulmonary hemartoma:
 - **It is the most common benign tumor of the lung.**
 - It has extremely slow growth:

Lung Cancer:

I. Introduction:

- It is the most frequently diagnosed major cancer.
- It is the most common cause of cancer mortality worldwide.
- **Risk Factors:**
 - Cigarette smoking:
 - It is the most important risk factor
 - It is responsible for at least 90% of lung carcinomas
 - Death rate in heavy smokers is 40 times that in non-smokers.
 - Passive-smoking is responsible for 5% of cancers.
 - Other Factors:
 - Radiation; Uranium
 - Asbestos; Arsenic; Radon
- **Cell Types:**
 - Small cell lung cancer (central location) = 20%
 - Non-small cell cancer:
 - Squamous cell carcinoma (central location) = 35% – most common
 - Adenocarcinoma (peripheral location) = 30%
 - Large cell carcinoma (peripheral location) = 15%

II. Clinical Presentation:

- **Cough - most common early symptom**
- Hemoptysis – common with central bronchial tumors.
- Chest pain; Weight loss; Dyspnea
- Mediastinal Spread:
 - Hoarseness - due to recurrent laryngeal nerve palsy
 - Dysphagia - due to esophageal invasion

- Bovine cough - cough lacking normal explosive character (recurrent laryngeal nerve palsy)
- Virchow's node - palpable left supraclavicular node
- SVC syndrome:
 - It results from compression of superior vena cava by tumor
 - It presents with head & neck swelling, conjunctival edema, headache, dilated veins on chest wall.
- Diaphragmatic paralysis from phrenic nerve invasion
- Bronchial obstruction:
 - Complete Obstruction:
 - Collapse of lung; presenting with:
 - Breathlessness, tracheal deviation towards the affected side
 - Dull percussion note on the affected side
 - Reduced breath sounds on the affected side.
 - Partial Obstruction:
 - Monophonic, unilateral wheeze that fails to clear with coughing.
 - Pneumonia and lung abscess.



Clinical Pearl:

Local Effects of Lung Cancer:

- "Horner's syndrome":
 - It is characterized by ipsilateral partial ptosis, enophthalmos, miosis, and anhidrosis.
 - It is due to involvement of sympathetic chain at or above the stellate ganglion.
- "Pancoast Syndrome":
 - It is caused by Pancoast tumor i.e. apical lung tumor in the superior pulmonary sulcus.
 - It is characterized by pain in shoulder and inner aspect of arm ± wasting of hand muscles.
 - It is due to damage to C8 – T1 roots of the brachial plexus.
 - It may be associated with Horner's syndrome.
- "Hypertrophic Pulmonary Osteoarthropathy":
 - It refers to periostitis of long bones (e.g. tibia, fibula, radius, and ulna).
 - It presents with pain and tenderness over the affected bones e.g. wrist pain.
 - It may be associated with digital clubbing.
 - X-ray reveals subperiosteal new bone formation.

III. Metastasis:

- Lymphatic spread = hilar lymph nodes (most common); mediastinal and cervical nodes
- Hematogenous spread:
 - Liver
 - Bone
 - Brain
 - Adrenals

IV. Paraneoplastic Syndromes:

- Cushing syndrome (ACTH) = Small cell cancer
- Syndrome of inappropriate ADH secretion = Small cell cancer
- Lambert-Eaton myasthenic syndrome = Small cell cancer
- Thrombophlebitis = Adenocarcinoma
- Nonbacterial verrucous endocarditis = Adenocarcinoma
- Hypercalcemia (PTH-related peptide) = Squamous cell
- Gynecomastia (gonadotropins) = Large cell cancer
- Digital clubbing = Non-small cell cancer
- Dermatomyositis = All of them
- Acanthosis nigricans = All of them

V. Investigations:

- Chest X-ray
- CT scan is useful for:
 - Detection of small tumors
 - Identifying disease in mediastinum, such as enlarged lymph nodes
 - Local spread of tumor
 - Secondary spread of carcinoma to opposite site lung.
- Positron Emission Tomography (PET):
 - It is the investigation of choice for:
 - Assessment of the mediastinum
 - Possible metastasis
- Fibreoptic Bronchoscopy:
 - It is used to define bronchial anatomy and to obtain biopsy and cytologic specimens.
 - It is used **for centrally located cancers.**
- Percutaneous Aspiration & Biopsy:
 - It is used (under CT guidance) **for peripherally located cancers.**
 - Most common complication = pneumothorax

VI.

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X**Management:**▪ **Non-Small Cell Lung Cancer:**

- Early stage = surgical resection (main treatment modality) plus adjuvant chemotherapy.
- Advanced stage:
 - **Chemotherapy** (main treatment modality) plus radiotherapy.
 - **Bevacizumab** (anti-vascular endothelial growth factor (VEGF) antibody) can increase median survival rate by 2 months.

▪ **Small Cell Lung Cancer (SCLC):**

- It is usually disseminated at presentation.
- **Chemotherapy – primary treatment modality**
- Radiotherapy added to chemotherapy improves survival.
- Prophylactic cranial irradiation improves survival.

Pulmonary Vascular Diseases

Pulmonary Embolism (PE):

I. Introduction:

- PE refers to thrombosis originating in venous system & embolizing to pulmonary arterial circulation.
- PE and deep venous thrombosis (DVT) is a continuum of one clinical entity i.e. venous thromboembolism.

▪ Source of Emboli:

- Lower Extremity DVT:
 - It is the most common source of emboli causing PE
 - Mostly arise from DVT above knee (ilio-femoral).
 - Deep veins of the pelvis
 - DVT of calf veins
- Upper Extremity DVT:
 - It is rare source of emboli.
 - It can be seen in IV drug abusers.

▪ Pathophysiology:

- Thrombus embolizes to the pulmonary vasculature via the RV and pulmonary artery.
- Blood flow distal to the embolus is obstructed, which leads to:
 - Increased pulmonary vascular resistance, pulmonary artery pressure.
 - Increased RV pressure, and if large, causes acute cor pulmonale.
- Dead Space is created in areas of lung that are ventilated, but not perfused.
- This leads to hypoxemia and hypercarbia, which increases respiratory drive – tachypnea.

▪ Risk Factors:

(Virchow's Triad):

- **Stasis** - bed rest, inactivity, CHF, stroke (within 3 mo), air travel > 6 hours
- **Injury to endothelium** - trauma, surgery, prior DVT, inflammation
- **Hypercoagulability:**
 - Protein C or S deficiency
 - Anti-phospholipid syndrome
 - Oral contraceptive pills (OCPs)
 - Hormone replacement therapy (HRT)

- Heparin-induced thrombocytopenia (HIT)
- Selective estrogen receptor modulators (SERMs) – Tamoxifen, Raloxifen
- Malignancy

II. Clinical Features:

- Sudden onset shortness of breath; clear lungs on examination
- Pleuritic chest pain
- Cough, hemoptysis
- Syncope (large PE)
- Signs:
 - Tachypnea; Tachycardia
 - Rales; S4
 - Decreased breath sounds, dullness on percussion
 - Low-grade fever

III. Investigation:

- **CXR:**
 - It is most commonly normal.
 - It is, however, essential to rule out other causes.
 - Most common abnormality = atelectasis
 - **Westermarck Sign** = focus of oligemia (vasoconstriction) seen distal to a pulmonary embolism (PE) – uncommon.
 - **Hampton's Hump** = wedge shaped, pleural based consolidation associated with pulmonary infarction – uncommon.
- **ABGs:**
 - Respiratory alkalosis – low PaO₂, low PaCO₂, high pH
 - Increased A-a gradient (normal A-a gradient makes PE less likely)
- **ECG:**
 - Most common finding = sinus tachycardia
 - Most common abnormality = non-specific ST – T wave changes.
 - Acute small PE = sinus tachycardia
 - Acute massive PE:
 - Anterior T-wave inversion
 - Right bundle branch block (RBBB)
 - **S1Q3T3 (i.e. right ventricular strain)** causing S-wave in Lead-I, Q-wave and inverted T-wave in Lead-III.
- **Lower Extremity Doppler Ultrasound:**
 - If the test is positive no further testing is needed.

- It is because the management of DVT & PE is the same, therefore, no need for CTA.
- If the test is negative, then it is of little value.
- Because, negative results occur in 50% of patients with proven PE.
- **CT – Angiography (CTA):**
 - It is the most commonly sought first-line diagnostic test.
 - It is the test of choice in most medical centers.
 - It can visualize very small clots (as small as 2 mm).
 - It cannot be performed in patients with significant renal insufficiency (requires IV contrast)
- **Pulmonary angiography:**
 - It is the gold standard investigation.
 - It involves contrast injection in to pulmonary artery branch after percutaneous catheterization of femoral vein.
 - It is invasive with significant mortality of 0.5%.
 - It is, therefore, now superseded by CT – angiography
- **D-dimer Level:**
 - It has a high negative predictive value.
 - It is performed when clinical suspicion for PE is low.
 - High D-dimer levels is of little clinical significance (can be seen in MI, CHF, pneumonia)
 - Low D-dimer levels (<500 ng/mL) helps RULE OUT the disease (particularly where clinical risk is low) – i.e. it has high sensitivity & low specificity.

IV.

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Management:

- Heparin and oxygen – it is the standard of care in PE.
- **Acute Anticoagulation Options:**
 - **Low-Molecular Weight Heparin (LMWH):**
 - It should be commenced immediately on the basis of clinical suspicion.
 - Do not wait for studies to confirm PE if clinical suspicion is high.
 - It reduces further propagation of clot and the risk of further emboli.
 - Agents:
 - Enoxaparin 1 mg/kg SC x twice daily.
 - Dalteparin 200 IU/kg SC x once daily
 - It should be given concurrently with warfarin for at least 5 days.

- It should not be discontinued until INR is ≥ 2 for at least 24 hours.
- **Fondaparinux:**
 - It is an alternative agent to LMWH.
 - It is given as 5 – 10 mg SC once daily.
 - It can be considered in patients who develop heparin-induced thrombocytopenia (HIT).
- **Thrombolytics:**
 - It used in hemodynamically unstable patients with acute massive PE.
 - It speeds up lysis of clots.
 - Agents: streptokinase, tissue plasminogen activator (tPA)
 - It carries risk of intracerebral hemorrhage with no mortality benefit.
- **Long-Term Anticoagulation Options:**
 - **Warfarin:**
 - It can be started with heparin on day 1.
 - Therapeutic INR is 2 – 3 (requires regular INR monitoring).
 - **Rivaroxaban:**
 - It is oral anticoagulant agent that does not require regular INR monitoring.
 - Advantages of rivaroxaban:
 - Acute Therapy – 15 mg PO x twice daily for 3 weeks (as effective as LMWH + warfarin)
 - Long-term Therapy – 20 mg once daily (as effective as long-term warfarin therapy)
 - **Duration of Anticoagulation:**
 - 3 – Months:
 - 1st distal DVT
 - 1st VTE event (proximal DVT or PE) secondary to reversible & time-limited risk factor
 - ≥ 3 – Months:
 - 1st unprovoked VTE event (proximal DVT or PE)
 - Males – have higher risk recurrent VTE than females
 - Elevated D-dimer levels 1 month after stopping anticoagulation
 - Indefinite (For Life):
 - 2nd VTE event
 - Those with persistent pro-thrombotic risk
 - Cancer-Associated VTE:
 - LMWH for 6 – months, then:
 - Switch to warfarin indefinitely (or until cancer cured)

○ **Inferior Vena Cava (IVC) Filter:**

- Indications:
 - Patients who have a contraindication to anticoagulation.
 - Patients who suffered massive hemorrhage on anticoagulation
 - Recurrent thromboembolism despite anticoagulation

Pulmonary Hypertension (PH):

- **"Definition":**
 - Mean pulmonary artery pressure > 25 mmHg at rest
 - Mean pulmonary artery pressure > 30 mmHg with exercise
 - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg
 - Pulmonary vascular resistance ≥ 240 dynes/s/cm⁵

I. Etiologies (Revised WHO Classification)

▪ **Group - 1:**

Pulmonary Arterial Hypertension (PAH):

○ **Pathophysiology:**

- Mutations in "morphogenetic protein receptor-2" (BMPR2):
 - Smooth muscle cell proliferation
 - Endothelial cell proliferation
- Imbalance b/w vasoconstrictors & vasodilators:
 - Increased vasoconstrictors – thromboxane A₂, serotonin, endothelin-1
 - Decreased vasodilators – prostacyclin, nitric oxide, vasoactive peptide

○ **Types:**

- Idiopathic (IPAH) – affects young people (20 – 30 years, mostly women)
- Familial (FPAH) – due to BMPR2 mutations
- Pulmonary veno-occlusive disease
- Associated Conditions (APAH):
 - Connective tissue disorders = SLE, RA, Sjogren's, MCTD, CREST
 - Congenital Left – Right shunts = ASD, VSD, PDA
 - HIV infection
 - Drugs and toxins
 - Thyroid diseases
 - Glycogen storage disease
 - Gaucher's disease
 - Hemoglobinopathies

- **Group – 2:**
Left – Sided Heart Disease:
 - LA & LV dysfunction (systolic or diastolic)
 - Left-sided valvular heart disease (e.g. MS, MR)
- **Group – 3:**
Lung Diseases & Chronic Hypoxemia:
 - COPD
 - Interstitial lung diseases
 - Alveolar hypoventilation (e.g. neuromuscular disease)
 - Chronic hypoxemia (e.g. high altitude)
 - Sleep apnea
 - Developmental abnormalities (e.g. severe kyphoscoliosis)
- **Group – 4:**
Chronic Thromboembolic Diseases:
 - Proximal & distal pulmonary embolisms
 - Non-thrombotic emboli – tumor, foreign body, parasites
 - Sickle cell disease
- **Group – 5:**
Miscellaneous:
 - Sarcoidosis
 - Histiocytosis X
 - Schistosomiasis
 - Compression of pulmonary vessels – (tumor, adenopathy, histoplasmosis, radiotherapy)

II. Diagnosis:

- **Clinical Features:**
 - Dyspnea, and exertional syncope – due to hypoxia & reduced cardiac output
 - Exertional chest pain – due to RV ischemia
 - Symptoms of RHF – tender hepatomegaly, peripheral edema, ascites
 - Signs:
 - Raised JVP (with prominent “a” wave if in sinus rhythm)
 - Parasternal heave (due to RVH)
 - Prominent pulmonary component of second heart sound
 - Right ventricular third heart sound
- **Investigations:**
 - ECG:
 - Right axis deviation; right bundle branch block

- Right atrial enlargement ("p" pulmonale); right ventricular hypertrophy
- **ABGs:**
 - Decreased PaO₂, SaO₂, and PaCO₂
 - Increased A – a gradient
- **CXR & High-resolution CT Chest:**
 - Dilatation and pruning of pulmonary arteries
 - Right atrial and ventricular hypertrophy
- **Trans-thoracic Echocardiography (TTE):**
 - Increased right ventricular systolic pressure
 - Tricuspid regurgitation; pulmonary regurgitation

III.

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Management:

- Pulmonary hypertension is incurable.
- **Supportive Measures:**
 - Oxygen: maintain SaO₂ > 90 – 92% (reduces vasoconstriction)
 - Diuretics (decrease right ventricular stress and relieve right heart failure)
 - Digoxin – control AFib
 - Anticoagulation with warfarin
- **Vasodilators:**
 - Calcium channel blockers (Nifedipine, Diltiazem):
 - These are used in patients with positive acute vasoreactive response.
 - These are associated with decreased mortality.

(**Positive Vasoreactive Response:** using inhaled nitric oxide, there is decreased pulmonary artery pressure ≥ 10 mm to a level < 40 mmHg with stable cardiac output. It helps identify patients who will benefit from CCB).
 - IV prostacyclin [i.e. prostaglandin (PG) I₂]:
 - It causes vasodilation, decreased platelet aggression & smooth muscle proliferation
 - Benefits increased with time – decreases mortality.
 - Endothelin Receptor Antagonists:
 - Agents – Bosentan, Ambrisentan

- Side-effects – deranged LFTs, headache, anemia, edema
- Phosphodiesterase-5 (PDE-5) Inhibitors:
 - These agents increase cGMP, which increases nitric oxide (vasodilation)
 - Agents – Sildenafil, Vardenafil
- **Refractory PHT:**
 - Lung transplant
 - Heart-lung transplant (if Eisenmenger's physiology)
 - Balloon Atrial Septostomy :
 - It result in R – L shunt (increases cardiac output, net tissue O₂ delivery)
 - It decompresses RV & improves hemodynamic performance

ARDS & Respiratory Failure

Acute Respiratory Distress Syndrome (ARDS)

I. Introduction:

- It is acute lung injury, resulting in release of inflammatory mediators causing increased capillary permeability and non-cardiogenic pulmonary edema, often accompanied by multi-organ failure.

Berlin Definition of ARDS:

- "Acute Onset"** – within 1 week of clinical insult or worsening respiratory status.
- "Bilateral Infiltrates on CXR"** – without alternative explanation (e.g. effusion, collapse, nodules)
- "Pulmonary Edema"** – not explained by fluid overload or congestive heart failure:
 - ARDS presents with non-cardiogenic pulmonary edema with PCWP < 18 mmHg
 - In cardiogenic pulmonary edema PCWP (pulmonary capillary wedge pressure) > 18 mmHg
- "Hypoxemia"** – $\text{PaO}_2/\text{FiO}_2$ determined with 5 cm H_2O of PEEP:
 - $\text{PaO}_2/\text{FiO}_2 = 300 - 200$: mild ARDS
 - $\text{PaO}_2/\text{FiO}_2 = 200 - 100$: moderate ARDS
 - $\text{PaO}_2/\text{FiO}_2 < 100$: severe ARDS

Clinical Pearl:

$\text{PaO}_2/\text{FiO}_2$:

- FiO_2 is fraction of inspired oxygen.
- FiO_2 is expressed as a decimal, so room air with 21% oxygen would be 0.21.
- If PaO_2 is 105 on room air (21% oxygen or 0.21), then $\text{PaO}_2/\text{FiO}_2$ is 500 ($105/0.21$).
- If PaO_2 as measured on ABG is 70 while breathing 50% oxygen, then the ratio is $70/0.5$ or 140.

II. Etiology:

Pathophysiology:

- Massive Intrapulmonary Shunting:
 - It is the key pathophysiologic event in ARDS.
 - It is due to widespread atelectasis, and surfactant dysfunction.
 - It results in hypoxemia with no improvement on 100% oxygen.

- It requires high PEEP to prop open the airways.
- Decreased pulmonary compliance – leads to increased work of breathing
- Increased dead space – due to obstruction & destruction of pulmonary capillary bed
- Low vital capacity & low FRC

▪ Causes:

- Direct Injury:
 - Pneumonia – most common (40%)
 - Aspiration (15%)
 - Inhalation injury
 - Near drowning
 - Lung contusion
- Indirect Injury:
 - Sepsis (25%)
 - Shock
 - Disseminated intravascular coagulation (DIC)
 - Pancreatitis
 - Trauma – Multiple fractures
 - Transfusion (Transfusion-related acute lung injury [TRALI])

III.

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Management:

- No treatment is proven to reverse ARDS.
- Treat the underlying the cause; give supportive therapy.

▪ Respiratory Support:

- Continuous positive pressure ventilation (CPAP) with 40 – 60% oxygen.
- But most patients need mechanical ventilation.
- Indications for mechanical ventilations are:
 - $\text{PaO}_2 < 8.3 \text{ kPa} (< 62 \text{ mmHg})$
 - $\text{PaCO}_2 > 6 \text{ kPa} (> 45 \text{ mmHg})$
- Mechanical Ventilation:
 - Use low-tidal volume mechanical ventilation.
 - **Maintain $\leq 6 \text{ mL/kg}$ of tidal volume (low-tidal volume).**
 - Maintain plateau pressure of $\leq 30 \text{ cm}$ of water (measured on ventilator)
 - **Keep $\text{FiO}_2 < 60\%$ i.e. 0.60 (higher levels are toxic to lungs)**

- Positive end-expiratory pressure (PEEP) is used when the patient is undergoing mechanical ventilation to try to decrease FiO_2 (if > 60%)
- **Circulatory support:**
 - Conservative fluid management.
 - **Target central venous pressure (CVP) = 4 – 6 cm H₂O**(if non-oliguric & normotensive)
 - BNP levels can be used to guide diuresis.
 - **If BNP > 200 consider diuresis (target urine output of 4.5–9 ml/kg/hr x 3 hours)**
 - This has shown to decrease the time to extubation.
- **Paralysis:**
 - Consider paralysis if $\text{PaO}_2/\text{FiO}_2 < 150$.
 - Agent – cisatracurium (neuromuscular blocking agent) x 48 hours (decreases mortality)
- **Steroids:**
 - Role of steroids continues to be controversial.
 - Its effect depends on the timing of administration as well.
 - Within 72 hours = decrease mortality; increase ICU-free days
 - 7 – 13 days = no mortality difference; increase ICU-free days
 - ≥ 14 days = increase mortality
- **Experimental Intervention:**
 - Inhaled nitric oxide = increases $\text{PaO}_2/\text{FiO}_2$, no mortality benefit
 - Inhaled prostacyclin = increases $\text{PaO}_2/\text{FiO}_2$, no mortality benefit
 - Prone ventilation = increases PaO_2 , but no mortality benefit
 - HF oscillatory vent. = high-frequency oscillatory vent. (no benefit, possible harm)
 - Lung Recruitment:
 - Apply CPAP 40 – 45 cm H₂O x 2 minutes to recruit lung
 - Then increase PEEP to maintain

Respiratory Failure:

I. Introduction:

- It refers to failure of pulmonary gas exchange required to maintain normal arterial oxygen and carbon dioxide levels.
- It is of two types depending upon the presence or absence of hypercapnia (raised PaCO_2).

<u>Type – I Respiratory Failure</u>		<u>Type – II Respiratory Failure</u>	
Hypoxia ($\text{PaO}_2 < 8 \text{ kPa}$ (60mmHg)) Normal or low $\text{PaCO}_2 (< 6.6 \text{ kPa}$ (50mmHg))		Hypoxia ($\text{PaO}_2 < 8 \text{ kPa}$ (60mmHg)) Raised $\text{PaCO}_2 (> 6.6 \text{ kPa}$ (50mmHg))	
<u>Acute</u>	<u>Chronic</u>	<u>Acute</u>	<u>Chronic</u>
<ul style="list-style-type: none"> ▪ Acute asthma ▪ ARDS ▪ Pulmonary edema ▪ Pulmonary embolism ▪ Pneumothorax 	<ul style="list-style-type: none"> ▪ Emphysema ▪ Lung fibrosis ▪ Lymphangitis carcinomatosa ▪ Right-to-left shunts ▪ Brainstem lesions 	<ul style="list-style-type: none"> ▪ Acute severe asthma ▪ Acute exacerbation of COPD ▪ Upper airway obstruction ▪ Acute neuropathies ▪ Narcotic drugs 	<ul style="list-style-type: none"> ▪ COPD ▪ Sleep apnea ▪ Kyphoscoliosis ▪ Myopathies ▪ Ankylosing spondylitis

II. Management of Acute Respiratory Failure:

- Prompt diagnosis and management of underlying cause.
- Type – I acute respiratory failure:
 - High concentration of oxygen (40 – 60% by mask)
 - Mechanical ventilation if patient doesn't respond with oxygen.
- Type – II acute respiratory failure:
 - With high ventilatory drive (i.e. rapid respiratory rate & accessory muscle recruitment)
 - Suspect acute upper airway obstruction from foreign body inhalation or laryngeal obstruction (e.g. angioedema, vocal cord paralysis).
 - In such cases Heimlich maneuver, immediate intubation, or emergency tracheostomy may be life-saving.
 - With low ventilatory drive or cannot move sufficient air:
 - Suspect problem in the lungs such as COPD, asthma, ARDS, pneumothorax.
 - In all such cases, high concentration oxygen (60%) should be administered.
 - Treat the underlying cause.
 - Indication for mechanical ventilation are:
 - Failure to respond to initial treatment.
 - Declining conscious level

- Worsening respiratory acidosis on blood gases ($\text{PaCO}_2 > 50$ mmHg)
 - Abnormal Tolerance to Raised PaCO_2 :
 - This develops in small percentage of patients with severe chronic COPD and type-II respiratory failure, and may become dependent on hypoxic drive to breathe.
 - In these patients only, lower concentration of oxygen (24 – 28% by Venturi mask) should be used to avoid precipitating worsening respiratory depression.

III. Management of Chronic & Acute on Chronic Type-II Failure:

- The most common cause of chronic type-II failure is severe COPD.
- The principal aim of treatment in acute on chronic type-II respiratory failure is to achieve a safe PaO_2 (> 7.2 kPa (52mmHg)) without increasing PaCO_2 and acidosis.
- Management:
 - Maintenance of airway
 - Treatment of specific precipitating cause
 - Frequent physiotherapy with or without pharyngeal suctioning
 - Nebulized bronchodilators
 - Controlled oxygen therapy:
 - Start with 24% Venturi mask
 - Aim for a $\text{PaO}_2 > 7$ kPa (52mmHg)
 - Antibiotics
 - Diuretics
 - Mechanical ventilation:
 - If PaCO_2 continues to rise
 - Patient cannot achieve a safe PaO_2 without severe hypercapnia and acidemia

Diseases of the Pleura

Pleural Effusion:

I. Introduction:

- It refers to accumulation of fluid in the pleural cavity.
- It is broadly classified as either “transudative” or “exudative”.
- Transudative Effusion:
 - It is caused by systemic factors
 - It is therefore bilateral and equal; pleural fluid pH is > 7.4 .
- Exudative Effusion:
 - It is caused by local factors, which alter pleural surface permeability.
 - It is therefore unilateral; pleural fluid pH is < 7.4 .

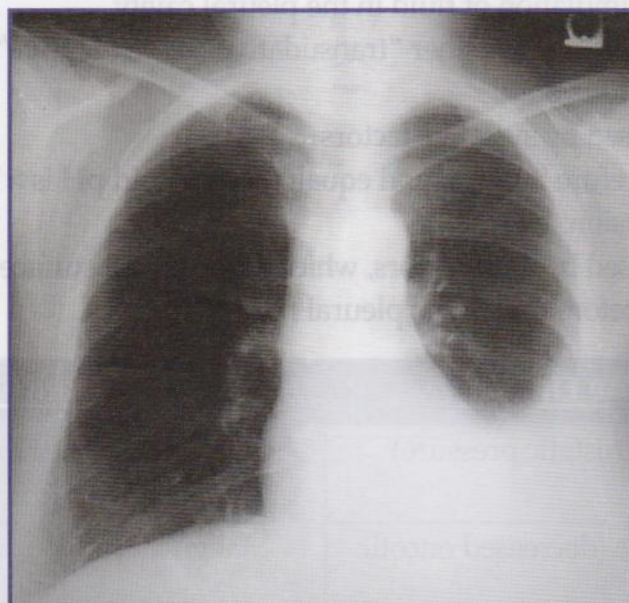
<u>Transudative Effusion</u>	<u>Exudative Effusion</u>
CHF (increased hydrostatic pressure)	Para-pneumonic effusion (pneumonia)
Nephrotic syndrome (decreased oncotic pressure)	Malignancy
Cirrhosis (decreased oncotic pressure)	Tuberculosis
Pulmonary embolism (1/3 rd cases)	Pulmonary embolism (2/3 rd cases)
Atelectasis	Collagen vascular disease (e.g. SLE, RA)
Malabsorption	Pancreatitis
Hypothyroidism	Esophageal rupture
Meig's syndrome (right pleural effusion + right ovarian fibroma)	Mesothelioma
Constrictive pericarditis	Lymphangitis carcinomatosa

II. Clinical Features:

- Asymptomatic
- Or may present with dyspnea, pleuritic chest pain
- Signs:
 - Decreased chest expansion
 - Stony dull percussion note
 - Diminished breath sounds
 - Tactile vocal fremitus and vocal resonance are decreased

III. Diagnostic Studies:

- Erect (PA) CXR:
 - Curved shadow at the lung base; blunting the costophrenic angle
 - Fluid appears to track up the lateral chest wall
 - Around 200 ml of fluid is required to be detectable on a PA chest X-ray.



CXR = Left-sided Pleural Effusion

- Thoracocentesis (Pleural Fluid Aspiration):
 - Indications = all effusions > 1 cm in decubitus view (CXR)
 - Transudate v/s Exudate:

Light's Criteria for Exudative Pleural Effusion

	<u>Transudative</u>	<u>Exudative</u>
LDH effusion	< 200 IU/ml	> 200 IU/ml
LDH effusion: serum ratio	< 0.6	> 0.6
Protein effusion: serum ratio	< 0.5	> 0.5
For transudative effusion all the 3 criteria must be present. Even if 1 criterion isn't met, then this is exudative effusion.		

III.

R_x**Management:**

- Treat the underlying cause e.g. :
 - Para-pneumonic effusion:
 - Uncomplicated = antibiotics for pneumonia
 - Complicated i.e. positive gram stain or culture, or pH < 7.2 or glucose < 60 = tube thoracostomy
- Drainage:
 - If the effusion is symptomatic.
 - It should be done slowly (≤ 2 L/day)
- Other Measures:
 - Pleurodesis with tetracycline or bleomycin for recurrent effusions
 - Surgery

IV. Pleural Fluid Analysis:

<u>Gross Appearance</u>	<u>Cause</u>
Clear, Straw-colored	Transudate, exudate
Turbid, yellow	Empyema, para-pneumonic effusion
Hemorrhage	Trauma, malignancy, pulmonary infarction
<u>Cytology</u>	<u>Cause</u>
Neutrophils ++	Para-pneumonic effusion, pulmonary embolism
Lymphocytes ++	Malignancy, TB, RA, SLE, sarcoidosis
Mesothelial cells ++	Pulmonary infarction
Abnormal mesothelial cells	Mesothelioma
Multi-nucleated giant cells	Rheumatoid arthritis
<u>Clinical Chemistry</u>	<u>Cause</u>
Protein < 25 g/L	Transudate
Protein > 25 g/L	Exudate
Glucose < 60 mg/dL	Empyema, malignancy, RA, TB, SLE
pH < 7.2	Empyema, malignancy, RA, TB, SLE
Raised LDH (pleural: serum > 0.6)	Empyema, malignancy, RA, TB, SLE
Raised amylase	Pancreatitis, esophageal rupture
<u>Immunology</u>	<u>Cause</u>
Rheumatoid factor	Rheumatoid arthritis
Anti-nuclear antibody	SLE
Decreased complement levels	RA, SLE, malignancy, infection

Empyema:

- It refers to collection of pus in the pleural space.
- It microscopically contains large numbers of neutrophils.

I. Causes:

- It is always secondary to infection of:
 - Para-pneumonic effusions (15%)
 - Tuberculosis
 - Hemothorax
 - Esophageal rupture
 - Rupture of subphrenic abscess

II. Clinical Features:

- It should always be suspected in patient with pulmonary infection if there is persisting or recurrent pyrexia despite treatment with suitable antibiotic.
- Systemic features:
 - High-grade, remittent fever
 - Rigors, sweating, malaise, and weight loss
 - Leukocytosis and high CRP
- Local Features:
 - Pleuritic chest pain
 - Breathlessness and productive cough
 - Clinical signs of pleural effusion

III. Diagnosis:

- CXR (may be similar to pleural effusion)
- Ultrasound
- CT scan of chest
- Aspiration of fluid:
 - US or CT is used to confirm the site of empyema.
 - Aspiration is best undertaken with wide-bore needle.
 - Features of empyema:
 - Thick and turbid pus
 - Fluid glucose < 3.3 mmol/L (60 mg/dL)
 - LDH > 1000 U/L
 - Fluid pH < 7.0

IV.

R_X**Management:**

- Non-tuberculous Empyema:
 - Wide-bore intercostal tube insertion under radiological guidance.
 - Tube is connected to underwater-seal drain system.
 - Empiric antibiotic therapy (e.g. IV cefuroxime + metronidazole) should be started.
 - Antibiotic therapy should be continued for 2 – 4 weeks.
 - Surgical decortication may be required in resistant cases.
- Tuberculous Empyema:
 - Start anti-tuberculous therapy with aspiration of pus by wide-bore needle.
 - Intercostal tube drainage is often required.

Pneumothorax:

- It refers to air in the pleural cavity.
- Clinical Findings:
 - Sudden onset of dyspnea
 - Pleuritic chest pain
 - Percussion note = tympanitic (resonant)
 - Breath sound = absent

(i). Spontaneous Pneumothorax:

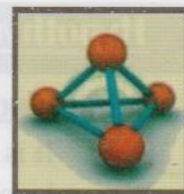
- Causes:
 - Idiopathic (most common)
 - Paraseptal emphysema
 - Marfan syndrome
- Pathogenesis:
 - Rupture of a subpleural bleb produces a hole in pleura.
 - Loss of negative intra-thoracic pressure and the lung collapses.
 - Trachea deviates to the side of lung collapse.

(ii). Tension Pneumothorax:

- Causes:
 - Penetrating chest wall injuries
 - Iatrogenic
 - Positive pressure ventilation
- Pathogenesis:
 - Flap-like pleural tear allows air into pleural cavity but prevents its exit
 - Increase in pleural cavity pressure.
 - Trachea deviates to the contralateral side of pneumothorax.

Chapter 7

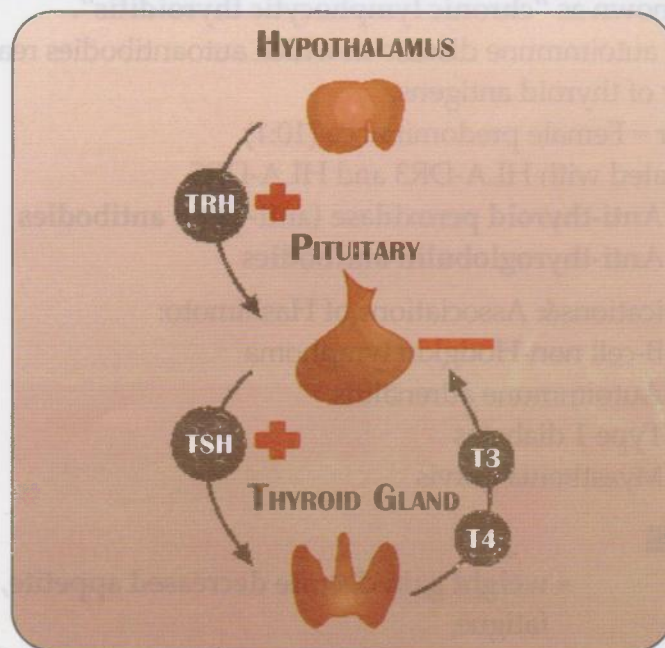
ENDOCRINOLOGY



Thyroid Disorders

Hypothalamic – Pituitary Control:

- Thyrotropin releasing hormone (TRH) is produced by hypothalamus.
- TRH stimulates the release of thyroid stimulating hormone (TSH) from anterior pituitary gland.
- TSH then acts on thyroid gland and increases both the synthesis and the secretion of thyroid hormones by thyroid follicular cells.
- Thyroid hormones are thyroxine (T4), and tri-iodothyronine (T3).
- T3 is more potent than T4.
- The target tissue converts T4 to T3.
- Thyroid hormones when elevated cause negative-feedback inhibition of TSH secretion from anterior pituitary by down-regulating TRH receptors in anterior pituitary.



Hypothalamic-Pituitary-Thyroid Axis:

+ Sign indicates stimulation

– Sign indicates inhibition

Hypothyroidism:

I. Introduction:

- It is caused by an abnormality that interferes with the production of adequate levels of thyroid hormones.
- **Causes:**

<u>Causes</u>	<u>Goiter</u>
Congenital Causes:	
▪ Dyshormogenesis	+
▪ Thyroid aplasia	-
Iodine deficiency	+
Hashimoto's thyroiditis	±
Iatrogenic:	
▪ Radioactive iodine ablation	±
▪ Thyroidectomy	-
▪ Amiodarone	±
▪ Lithium	±
▪ Anti-thyroid drugs	±

▪ **Hashimoto's Thyroiditis:**

- It is the most common cause of hypothyroidism.
- Also known as "**chronic lymphocytic thyroiditis**".
- It is an autoimmune disease in which autoantibodies react against a variety of thyroid antigens.
- Gender = Female predominance (10:1)
- Associated with HLA-DR3 and HLA-DR5.
 - **Anti-thyroid peroxidase (anti-TPO) antibodies** = positive
 - **Anti-thyroglobulin antibodies** = positive
- Complications& Associations of Hashimoto:
 - B-cell non-Hodgkin lymphoma
 - Autoimmune adrenalitis
 - Type 1 diabetes
 - Myasthenia gravis

II. Clinical Features:

- General = **weight gain despite decreased appetite, cold intolerance, fatigue,**
- Skin = **dry skin, dry hair, alopecia,**

- Heart = **diastolic hypertension**, bradycardia
- Neurologic depression = **carpal tunnel syndrome**, delayed relaxation of reflexes,
- Reproductive = **menorrhagia**, infertility, impotence
- Gastrointestinal = constipation, ileus

III. Diagnosis:

Thyroid Function Tests (TFTs)

- Normal values: TSH = 0.5 – 5 mU/L, T4 = 4.5 – 12 µg/dl, T3 = 115 – 190 ng/dl.
- **TSH is the most useful investigation of thyroid function (both hypo- and hyperthyroidism).**
 - Primary hypothyroidism:
 - The gland itself is abnormal – most common type (> 90%)
 - Decreased T3, T4, increased TSH,
 - Secondary hypothyroidism:
 - The source is pituitary gland failure.
 - Decreased T3, T4, decreased TSH
 - Tertiary hypothyroidism:
 - The source is hypothalamus failure.
 - Decreased T3, T4, decreased TSH

Other Tests:

- Increased creatinine kinase (CK)
- Increase lactate dehydrogenase (LDH)
- Increased aspartate transaminase (AST)
- Increased cholesterol
- Decreased sodium
- ECG:
 - Sinus bradycardia with small complexes
 - ST – T wave abnormalities

III.

R_x**Treatment:**

- Replacement Therapy:
 - Life-long treatment with levothyroxine.
 - Dosage (1.5 – 1.7 µg/kg/day)
 - Example:
 - 50 µg/day for 3 weeks, then:
 - 100 µg/day for 3 weeks, then:
 - 100 – 150 µg/day as a maintenance dose thereafter
- Monitoring:
 - The aim is to restore TSH to well within normal range.
 - The effect of medication is evident within 2 – 3 weeks.
 - Levothyroxine has a half-life of 7 days.
 - It is given as single daily dose.
 - TFTs should be performed **after at least 6 weeks** to assess for the adequacy of treatment.
 - If serum TSH remains high, the dose of thyroxin should be increased.
 - Absorption of drug is increased:
 - If taken before bed.
 - If taken along with vitamin C supplements
- Starting Dose in Special Patients:
 - (i). Ischemic Heart Disease & Elderly:
 - Levothyroxine increases myocardial O₂ demand – can precipitate angina or MI.
 - The starting dose should be low ≈ 25 µg/day (0.3 – 0.5 µg/kg/day).
 - The dose should be increased very slowly under specialist supervision.
 - (ii). Pregnant Women:
 - In pregnancy, there is increased serum thyroxin-binding globulin (TBG).
 - Therefore, pregnant women require an increased dose by 25 – 50 µg to maintain normal TSH.
 - Inadequate maternal levothyroxine therapy can cause cognitive impairment in the developing fetus.



Clinical Pearl: **Levothyroxine Therapy:**

- Increased dose of levothyroxine is required in following conditions:
 - Pregnancy (increases TBG)
 - Estrogen therapy (increases TBG)
 - Medications that increase T4 catabolism:
 - Phenytoin, Phenobarbital
 - Carbamazepine, Rifampicin
 - Poor Gastrointestinal Absorption:
 - Concomitant iron & calcium supplements
 - Proton pump inhibitors, Sucralfate
 - IBD, Celiac Disease
 - Cholestyramine

IV. Myxedema Coma:

- It is a rare manifestation of severe hypothyroidism; usually in the elderly.
- It is a **medical emergency**, associated with 50% mortality rate.
- **Treatment must begin before biochemical confirmation of diagnosis.**
- **Clinical Features:**
 - Hypothermia; Hypotension (CHF)
 - Hypoventilation; Hypoglycemia
 - Hyponatremia
 - Altered level of consciousness.
 - CSF:
 - Pressure increased
 - Protein increased



Treatment:

- Tri-iodothyronin (T3):
 - IV bolus of 20 µg followed by 20 µg 8-hourly.
 - After 48 – 72 hours, oral thyroxine (50µg daily) may be started.
- Empiric adrenal replacement therapy – Hydrocortisone 100 mg IV 8-hourly.
- Gradual rewarming
- Broad-spectrum antibiotics
- High-flow oxygen with or without assisted ventilation

Hyperthyroidism:

I. Introduction:

- Thyrotoxicosis is a constellation of clinical features arising from elevated circulating levels of thyroid hormones.
- Causes:
 - Grave's disease – most common cause
 - De Quervain thyroiditis
 - Painless thyroiditis
 - TSH – secreting pituitary tumor
 - Toxic adenoma
 - Factitious thyrotoxicosis (exogenous thyroxin intake)
 - Miscellaneous:
 - Amiodarone
 - Struma Ovarii (ovarian dermoid tumors and teratomas)

II. Clinical Features:

- General = **weight loss despite increased appetite, heat intolerance, fatigue,**
- Skin = **sweaty, pruritis, palmar erythema, pretibial myxedema**
- Heart = **systolic hypertension, tachycardia**
- Neurologic = **anxiety, irritability, hyper-reflexia, tremors, ill-sustained clonus**
- Reproductive = **oligomenorrhoea, infertility, impotence**
- Gastrointestinal = **hyperdefecation, diarrhea**
- Ocular = **grittiness, diplopia, lid-retraction, lid-lag**

III. Graves' Disease:

- It is an autoimmune disease associated with thyrotoxicosis and hyperthyroidism.
- It is the most common cause of endogenous hyperthyroidism.
- **Epidemiology:**
 - Age = 30 – 50 years
 - Female predominance (7:1)
 - Family history
 - HLA-B8 and HLA-DR3
 - Smoking = weakly associated with Grave's thyrotoxicosis
 - Smoking = strongly associated with development of ophthalmopathy.
- **Pathogenesis:**
 - It is type-II hypersensitivity reaction, in which IgG antibodies (Thyroid-stimulating immunoglobulin (TSI)) act on TSH-receptors on follicular cells and mimics action of TSH, causing continuous stimulation of thyroid gland.

- These **TSH-receptor antibodies (TRAb)** can be detected in 80 – 90% of patients.
- The presence of other thyroid antibodies is NOT helpful in making a diagnosis.
- **Clinical findings:**
 - All the features of hyperthyroidism (discussed above)
 - Goiter = diffuse, non-tender, with thyroid bruit.
 - Exophthalmos:
 - Lid-lag and lid retraction can be seen in all causes of hyperthyroidism.
 - Exophthalmos (proptosis) is however, seen ONLY in Grave's disease
 - T-cell infiltration of retro-orbital space.
 - Edema of extraocular muscles
 - Accumulation of glycosaminoglycans
 - Increased number of adipocytes (fatty infiltration)
 - Infiltrative dermopathy:
 - Also called pretibial myxedema
 - It presents with raised pink-purplish plaques on skin overlying the shins.
 - It is seen in < 10% of patients with Graves' disease.
 - It due to excess glycosaminoglycans in dermis.
- **Diagnosis:**
 - Unique feature = diffuse goiter, ophthalmopathy, dermopathy
 - TFTs = increased T4, T3, decreased TSH
 - RAIU = bilateral, diffuse increased uptake
 - TRAb = positive.



Clinical Pearl: **Hyperthyroidism:**

- ALL forms of hyperthyroidism are associated with elevated T4 levels.
- ALL forms of hyperthyroidism are associated decreased TSH, EXCEPT for secondary hyperthyroidism (pituitary).

Radioactive I₂ uptake (RAIU):

- Increased uptake in whole gland (diffusely) = Graves' disease.
- Increased uptake in a solitary nodule (hot spot) = Toxic adenoma.
- Low, patchy uptake within nodules = Multinodular goiter
- Decreased uptake = Thyroiditis

IV. Hyperthyroidism & Pregnancy:

- In pregnant women, trimester-specific reference ranges of TSH should be used for interpretation.
- It is because in pregnancy TBG is increased, therefore, total T3 & T4 are also elevated.
- This helps differentiates normal TFTs during pregnancy from thyrotoxicosis.
 - Best screening test= TSH only
 - TSH Adjust levels:
 - 1st Trimester = 0.1 – 2.5
 - 2nd Trimester = 0.2 – 3.0
 - 3rd Trimester = 0.3 – 3.0
- Effects of Uncontrolled Thyrotoxicosis on Fetus:
 - Fetal tachycardia, Intrauterine growth retardation (IUGR)
 - Prematurity, Stillbirth, Congenital malformation

V.

R_x

Treatment:

▪ Beta-Blockers:

- They decrease peripheral conversion of T4 to T3.
- These are highly effective for symptomatic relief (tachycardia, tremors)
- Agents: non-selective β -blockers (propranolol 160 mg daily, nadolol 40–80 mg daily)

▪ Anti-Thyroid drugs:

- The half-life of T4 is 7 days:
 - It takes 10–14 days for drugs to show clinical benefit.
 - It takes 3 – 4 weeks to render patients clinically & biochemically euthyroid.
- Agents (along with starting dose):
 - Carbimazole (40 – 60 mg daily)
 - Methimazole (40 – 60 mg daily)
 - Propylthiouracil (PTU) – (400 – 600 mg daily)
(starting dose should be high)
- Complications:
 - Hypersensitivity rash – most common
 - Agranulocytosis – most dangerous
 - Methimazole = arthralgia, fever
 - PTU = hepatocellular necrosis

- Pregnancy:
 - **Anti-thyroid drugs are the treatment of choice for thyrotoxicosis in pregnancy.**
 - Anti-thyroids cross placenta and will treat thyrotoxicosis in fetus caused by transplacental passage of TRAb.
 - Anti-thyroids should be started at smallest dose possible that effectively keeps T3, T4, & TSH within reference range – to prevent fetal hypothyroidism.
 - Management:
 - Radioactive iodine = Absolutely contraindicated
 - 1st trimester = PTU (because Methimazole is teratogen)
 - 2nd & 3rd trimester = Methimazole (because PTU is associated with liver failure)
- **Radioactive Iodine (RAI):**
 - It is administered as a single oral dose.
 - Contraindications:
 - Absolute = pregnancy
 - Relative = ophthalmopathy:
 - RAI can worsen ophthalmopathy.
 - It can be prevented by prophylactic steroid administration.
 - Rules for RAI:
 - Patients must be rendered euthyroid before treatment.
 - Stop anti-thyroid drugs at least 4 days before, and not to commence until 3 days after RAI.
 - Patients on PTU should stop anti-thyroid drugs earlier than those on carbimazole, because it has a radio-protective action.
 - Complications:
 - Hypothyroidism – most common
 - Worsens ophthalmopathy



Clinical Pearl: **Radioactive Iodine:**

- Pregnancy is an absolute contraindication for RAI therapy.
- Women should be advised to avoid pregnancy for 6 months post-RAI therapy.
- Men should be advised to avoid fathering a child for 6 months post-RAI therapy.

▪ **Surgery (sub-total thyroidectomy):**

- Patients must be rendered euthyroid before treatment.
- Stop anti-thyroid drugs 14 days before surgery.
- Start potassium iodide (60 mg three times daily) for remaining 14 days before surgery. It reduces the vascularity of the gland.
- Complications:
 - Hypothyroidism – most common
 - Transient hypocalcemia
 - Hypoparathyroidism
 - Recurrent laryngeal nerve paralysis



Clinical Pearl:

Choice of Therapy:

- Indications for either surgery or radioactive iodine are:
 1. Patient choice
 2. Persistent drug side-effects
 3. Poor compliance with drug therapy
 4. Recurrent hyperthyroidism after drugs.
 5. Large goiter (surgery)

VI. Thyroiditis & Other Causes of Hyperthyroidism:

▪ **Silent Thyroiditis:**

- It is also known as “**Subacute Lymphocytic Thyroiditis**” or “**Painless Thyroiditis**”.
- It is characterized by transient hyperthyroidism, followed sometimes by hypothyroidism, and then recovery.
- It is an autoimmune disease and considered a variant of Hashimoto’s thyroiditis (i.e. the transient hyperthyroid state of Hashimoto’s – “**Hashitoxicosis**”).
- Treatment = no treatment
- Diagnosis:
 - TFTs = elevated T3, T4, decreased TSH
 - RAIU = decreased
 - Unique Feature = **painless thyroiditis, positive thyroid peroxidase & thyroglobulin antibodies.**

▪ **De Quervain Thyroiditis:**

- It is also known as “**Subacute Granulomatous Thyroiditis**”.

- It is thought to be caused by a viral infection such as Coxsackievirus, Adenovirus, Measles, and Mumps.
- Diagnosis:
 - **Thyroid gland is enlarged, palpable, & painful**
 - **Neck pain radiates to the angle of jaw and the ears.**
 - Neck pain is aggravated by swallowing, coughing, and movement of neck.
 - Affected patients are females 20 – 40 years
 - Hyperthyroidism (4 – 6 weeks), followed by hypothyroidism (variable period), then recovery (within 4 – 6 weeks).
 - **Elevated erythrocyte sedimentation rate (ESR).**
 - TFTs = elevated T3, T4, decreased TSH
 - RAIU = decreased
- Treatment:
 - Mild – Moderate Cases = NSAIDs, aspirin
 - Sever Cases = Prednisolone (40 mg daily for 4 weeks)
 - Anti-thyroid drugs = No benefit (thyroid hormone synthesis is impaired)
- **Post – Partum Thyroiditis:**
 - Definition:
 - **Thyroiditis induced by an autoimmune mechanism within 1 year after delivery**
 - It can also occur after occur after spontaneous or induced abortion.
 - Clinical Features:
 - Transient hyperthyroidism alone – OR
 - Transient hypothyroidism alone – OR
 - Transient hyperthyroidism, followed by hypothyroidism, then recovery
 - It tends to recur after subsequent pregnancies.
 - **It eventually progresses over a period of years to permanent hypothyroidism.**
 - Diagnosis:
 - Elevated T4, Depressed TSH (during hyperthyroid state)
 - High thyroglobulin; Low RAIU (like any other thyroiditis)
 - Treatment:
 - Hyperthyroid State:
 - Asymptomatic women = no treatment
 - Symptomatic women = beta blockers (short course, gradually tapered off)
 - Anti-thyroid drugs = no benefit

- Hypothyroid State:
 - Asymptomatic women = no treatment
 - Symptomatic women = levothyroxine (6-12 mo, gradually tapered off)
- **TSH – Secreting Pituitary Adenoma:**
 - It causes secondary hyperthyroidism i.e. it is the ONLY cause of hyperthyroidism with an elevated TSH.
 - Treatment = Brain MRI, followed by surgical removal of adenoma.
 - Diagnosis:
 - Elevated T3, T4
 - Elevated TSH
- **Factitious Thyrotoxicosis:**
 - It refers to consuming excessive amounts of thyroid hormone, most often levothyroxine.
 - Diagnosis:
 - TFTs = increased T4, decreased TSH
 - RAIU = decreased
 - Thyroid gland = atrophied
 - T4: T3 ratio:
 - In other causes of thyrotoxicosis the ratio is 30: 1
 - **In factitious thyrotoxicosis the ratio is increased to 70: 1.**
 - This is because in factitious thyrotoxicosis circulating T3 is derived exclusively from peripheral conversion of T4 and not from thyroid secretion.



Clinical Pearl:

RAIU + Thyroglobulin:

- All forms of thyroiditis are associated with decreased RAIU.
- All forms of thyroiditis are associated with increased thyroglobulin (∴ there is gland destruction).
 - **Low RAIU + Low Thyroglobulin = Factitious Thyrotoxicosis**
 - **Low RAIU + High Thyroglobulin = Thyroiditis**
 - **High RAIU + High Thyroglobulin = Graves's disease**

VII. Important Manifestations of Thyrotoxicosis:

Thyroid Storm:

- It is a medical emergency, with mortality rate of 10%.
- Clinical Features:
 - Fever; tachycardia
 - Agitation; confusion
 - Systolic hypertension, but wide pulse pressure
 - Atrial fibrillation and CHF.



Treatment:

- Beta blocker (propranolol) orally or intravenously.
- Sodium ipodate – restores serum T3 levels to normal in 48-72 hours by:
 - Inhibiting release of hormones.
 - Inhibiting conversion of T4 to T3.
- Oral PTU or carbimazole – blocks production of thyroxine
- With or without steroids – blocks peripheral conversion of T4 to T3.

Atrial Fibrillation (AF):

- It is present in 10% of all patients with thyrotoxicosis.
- Treatment:
 - Rate control = beta blocker (agent of choice); digoxin
 - Anticoagulation with warfarin

Thyroid (Grave's) Ophthalmopathy:

- It is typically episodic.
- It is detectable in 50% of thyrotoxic patients at presentation.
- It can worsen after RAI, but can be prevented by prophylactic steroids.
- Treatment:
 - Methylcellulose eye drops for dry eyes
 - Sunglasses to reduce lacrimation.
 - Steroids
 - Irradiation
 - Surgical decompression of the orbit.

VIII. Amiodarone & Thyroid Disease:

- It is a class-III anti-arrhythmic drug.
- It contains large amount of iodine.
- It causes both hyperthyroidism (15%) and hypothyroidism (85%).

▪ Hyperthyroidism:

○ Type-I Amiodarone-induced Thyrotoxicosis (AIT):

- It is associated with pre-existing Grave's disease or multi-nodular goiter.
- Pathophysiology = **Jod-Basedow Effect** i.e. iodine load of the drug stimulates synthesis of T4 & T3 in autonomous tissue.
- Doppler ultrasound = increased thyroid blood flow.
- Treatment = anti-thyroid drugs (Methimazole)

○ Type-II Amiodarone-induced Thyrotoxicosis (AIT):

- It is not associated with previous thyroid disease.
- It is due to direct effect of drug on thyroid follicular cells causing destructive thyroiditis.
- Pathophysiology = the drug stimulates the release of **pre-formed T4 & T3** causing hyperthyroidism.
- Doppler ultrasound = decreased thyroid blood flow.
- Treatment = steroids (anti-thyroid drugs not useful)

Clinical Pearl:

Types of AIT:

- Practically it is difficult to distinguish the two types of AIT.
- In such cases, start anti-thyroid drugs + steroids:
 - Rapid response (1–2 weeks) – suggests Type-II AIT (you can then gradually stop anti-thyroid drugs & continue steroids)
 - Delayed response – suggests Type-I AIT (you can then stop steroids and continue anti-thyroid drugs)

▪ Hypothyroidism:

- Mechanisms:
 - Blocks peripheral conversion of T4 to T3.
 - Immune-mediated thyroid destruction
 - **Wolff–Chaikoff Effect** i.e. iodine load of drug causes decreased iodide uptake, organification, and release of T4 & T3.
- Manifestation:
 - Normal individuals:
 - Decreased T4, then they escape Wolff–Chaikoff effect and have increased T4, decreased T3 and increased TSH.
 - Then TSH normalizes after 1 – 3 months.

- Susceptible Individuals:
 - These patients (e.g. subclinical Hashimoto's) do not escape Wolff–Chaikoff effect and therefore develop features of hypothyroidism.
 - Treatment = thyroxine replacement (can be given while amiodarone is continued).

Thyroid Nodule & Thyroid Neoplasia:

I. Thyroid Nodule:

- Prevalence = 5 – 10%.
- Features of thyroid nodule that point towards increased risk of malignancy are:
 - Male gender
 - Age < 20 or > 70 years
 - Family history of thyroid cancer
 - History of neck irradiation
 - Cold nodule i.e. decreased RAIU.
 - Hard (firm), fixed mass
 - Worrisome US findings:
 - Hypoechoic, solid, irregular borders
 - Micro-calcifications, central blood flow
- Management:
 - The best initial test is thyroid function tests (TFTs).
 - If TFTs are normal then the most appropriate next step is fine-needle aspiration (FNA).
 - If FNA shows malignant features then it should be surgically removed.
 - If TFTs show hyperthyroidism (i.e. a hyper-functioning nodule) then immediate FNA is not indicated because hyper-functioning nodule is mostly benign.
 - For hyper-functioning nodule the best next step is RAIU:
 - If uptake is low i.e. cold nodule = perform FNA
 - If uptake is high i.e. hot nodule = likely to be a benign nodule or toxic adenoma.

II. Thyroid Neoplasia:

- **Papillary Carcinoma:**
 - It is the **most common thyroid cancer** (75–85%)
 - Risk factor = ionizing radiation;
 - Age = any age (20 – 40 years)
 - Gender = female dominant; Prognosis = excellent

- Metastasis:
 - **Lymphatic spread occurs first.**
 - Hematogenous spread to lungs (most common)
- Diagnosis:
 - **Psammoma bodies** i.e. dystrophically calcified cancer cells.
 - **Orphan Annie eye nuclei** i.e. empty appearing nuclei (diagnostic feature).
- Treatment:
 - Total thyroidectomy, followed by large dose of radioactive iodine.
 - Long-term treatment with thyroxine (to suppress TSH).
 - Follow-up is by **measurement of serum thyroglobulin**, which must be undetectable.
 - If thyroglobulin is detectable it suggests tumor recurrence or metastases.
- **Follicular Carcinoma:**
 - It is the second most common thyroid cancer (10–20%)
 - Risk factor = iodine deficiency;
 - Age = older than papillary
 - Gender = female dominant
 - **Capsular & vascular invasion differentiates it from follicular adenoma**
 - **Hematogenous spread occurs first.**
 - Treatment = same as papillary carcinoma.
- **Medullary Carcinoma:**
 - It is a neuroendocrine neoplasm derived from **parafollicular cells (C-cells)**.
 - It is sporadic in 80% of cases, while familial types are associated with multiple endocrine neoplasia-2 (**MEN-2**) syndromes.
 - Clinical presentation:
 - Mass in neck; Dysphagia and hoarseness
 - Diarrhea (due to vasoactive intestinal peptide (VIP))
 - C-cells of medullary carcinomas, similar to normal C-cells secrete calcitonin.
 - Serum calcitonin is raised, but hypocalcemia is not prominent.
 - **Measurement of calcitonin** plays an important role in the diagnosis and post-operative follow-up of patients.
 - Treatment:
 - Total thyroidectomy, PLUS
 - Removal of cervical nodes

▪ **Anaplastic Carcinoma:**

- It is undifferentiated tumor of thyroid follicular epithelium.
- It accounts for less than 5% of all thyroid cancers.
- It is the **most aggressive tumor**, with a mortality rate of 100%.
- Clinical course:
 - Rapidly enlarging bulky mass.
 - Stridor (compression of trachea)
 - Hoarseness (recurrent laryngeal nerve palsy)
 - Metastasis = lungs.
 - Cause of death = compression of vital structures in neck.

Asymptomatic Abnormal TFTs:

I. Subclinical Thyrotoxicosis:

- It is most commonly seen in elderly patients with multinodular goiter
- It is associated with increased risk of AFib, cardiovascular disease and osteoporosis.
- TFTs:
 - TSH = decreased (undetectable)
 - Serum T3 & T4 = upper normal range
- Treatment:
 - It is controversial.
 - It should be considered in patients with:
 - TSH < 0.1 mU/l
 - Increased risk for CV disease or osteopenia

II. Subclinical Hypothyroidism:

- TFTs:
 - TSH = elevated
 - Serum T3 & T4 = lower normal range
- Progression to overt thyroid failure is highest in those with:
 - Ant-thyroid peroxidase antibodies
 - TSH > 10 mU/l.
- Treatment:
 - It is controversial.
 - It is indicated (levothyroxine) in patients with:
 - TSH > 10 mU/l
 - Anti – TPO antibodies
 - Symptomatic
 - Goiter

- Ovulatory & menstrual dysfunction (infertility)
- Dyslipidemia

III. Sick Euthyroid Syndrome:

- Also known as “Non-Thyroidal Illness” or “Low T3 Syndrome”.
- It refers to TFT abnormalities in patients with severe non-thyroidal illness.
- It results because during illness there is decreased conversion of T4 to T3 & alterations in affinity to binding proteins.
- TFTs should therefore not be checked during an acute illness in the absence of clear signs of thyroid disease.
- TFTs:
 - TSH = undetectable
 - T4 = raised
 - T3 = low, normal, or raised

Parathyroid Glands & Calcium Disorders

Normal Physiology:

- Functions of Parathyroid Hormone (PTH):
 - Activates osteoclasts, thereby mobilizing bone calcium.
 - Increases renal tubular reabsorption of calcium.
 - Increases gastrointestinal absorption of calcium.
 - Increases urinary phosphate excretion.
 - Net Effect:
 - Increased serum free calcium, which in turn inhibits further PTH secretion.
 - Decreased serum phosphate.

Hyperparathyroidism:

- It is a condition due to increased PTH production, resulting in hypercalcemia.
- Most common cause of asymptomatic hypercalcemia is primary hyperparathyroidism.
- Most common cause of clinically apparent hypercalcemia is malignancy.

I. Primary Hyperparathyroidism:

- It is characterized by autonomous secretion of PTH.
- Causes:
 - Parathyroid adenoma (most common) – 80%
 - Parathyroid primary hyperplasia
 - Parathyroid carcinoma
- Clinical Features:
 - **“Painful bones, renal stones, abdominal groans, and psychic moans”.**
 - Painful bones = osteoporosis, fractures, Osteitis fibrosa cystica (“brown tumors”)
 - Renal stones = due to hypercalciuria; nephrocalcinosis
 - Abdominal groans = peptic ulcer, gallstones, constipation (due to hypercalcemia)
 - Psychic moans = depression, lethargy, seizures
- Lab Findings:
 - Increased PTH, increased serum calcium (hypercalcemia), decreased phosphate.
 - Increased alkaline phosphatase, increased urinary cAMP.

Rx

Treatment:

- Surgical removal is the treatment of choice.
- Indications for surgery:
 - Any symptomatic disease
 - Asymptomatic Patients:
 - Age < 50 years
 - Renal insufficiency (creatinine clearance [CrCl] < 60 ml/minute)
 - DEXA T-score < - 2.5
 - Elevated serum calcium:
 - > 1 mg/dL above upper normal range – OR
 - Corrected serum calcium > 11.4 mg/dL
- If Surgery Declined (Deferred):
 - Bisphosphonates = increase bone mineral density, but do not decrease Ca & PTH
 - Cinacalcet = decreases Ca & PTH, may not increase bone mineral density.

Clinical Pearl:

Surgery for Primary Hyperparathyroidism:

- Parathyroid Adenoma = Surgical removal of adenoma
- Parathyroid Carcinoma = Surgical removal of tumor + ipsilateral thyroid lobe + all enlarged lymph nodes.
- Parathyroid Hyperplasia:
 - Surgical removal of all 4 parathyroid glands.
 - Small amount of parathyroid tissue is placed in the forearm muscle
(to retain parathyroid function)

II. Secondary Hyperparathyroidism:

- It refers to secondary hyperplasia of parathyroid gland caused by any condition that decreases serum calcium.
- Causes:
 - **Chronic renal failure – most common cause**
 - Vitamin D deficiency
 - Malabsorption – Steatorrhea
 - Decreased dietary intake of calcium.

▪ **Diagnosis:**

- Symptoms associated with chronic renal failure.
- **Calciophylaxis:**
 - Ischemia and necrosis of skin and other organs.
 - It is due to metastatic calcification of blood vessels.
- Increased PTH, decreased serum calcium (hypocalcemia), increased phosphate.
- Increase alkaline phosphatase.

<u>Condition</u>	<u>Serum Calcium</u>	<u>Serum Phosphate</u>	<u>PTH</u>
Primary hyperparathyroidism	↑	↓	↑
Secondary hyperparathyroidism	↓	↑	↑
Tertiary hyperparathyroidism	↑	↑	↑

III. Tertiary Hyperparathyroidism:

- It refers to refractory (autonomous) hyperparathyroidism resulting from chronic renal failure.
- It is seen in patients with prolonged secondary hyperparathyroidism, in which continuous stimulation of parathyroids results in adenoma formation and autonomous PTH secretion.
- **Diagnosis:**
 - Increased PTH.
 - Increased calcium and phosphate.

Hypoparathyroidism:

- It refers to decreased PTH secretion, resulting in **hypocalcemia**.
- **Causes:**
 - Surgical removal.
 - Congenital absence.
 - DiGeorge syndrome.
 - Familial
 - Idiopathic
- **Clinical Features:**
 - Depression and hallucinations
 - Cataract formation

- Prolonged Q – T interval
- Dental hypoplasia and failure of eruption.
- Tetany
 - **Chvostek's sign i.e.** tapping of facial nerve causes contraction of facial muscles.
 - **Trousseau's sign i.e.** occlusion of brachial artery with BP cuff causes carpal spasm.

▪ **Pseudo-Hypoparathyroidism:**

- It is an autosomal dominant condition in which **PTH production is normal**, but the kidneys are unresponsive to PTH.
- **"Albright's Hereditary Osteodystrophy (AHO)":**
 - It is type-1a pseudo-hypoparathyroidism.
 - It is caused by mutations encoding G-protein (GNAS1, signal transducer for PTH receptor) inherited on MATERNAL chromosome.
 - It is characterized by:
 - Short stature
 - **Short 4th & 5th metacarpals and metatarsals.**
 - Rounded face; obesity
 - Calcification of basal ganglia.
 - Hypocalcemia, Hyperphosphatemia
 - Increased serum PTH
- **"Pseudo-Pseudohypoparathyroidism":**
 - It is characterized by all features of AHO, but normal serum Ca & PTH
 - It is caused by mutations encoding G-protein (GNAS1) inherited on PATERNAL chromosome.

Calcium Disorders:

I. Hypercalcemia:

- It refers to serum calcium level of > 10.2 mg/dL.
- **Causes:**
 - **Appropriate Hypercalcemia:** (i.e. hypercalcemia with low PTH)
 - Malignancy – most common cause
 - Vitamin D intoxication
 - Granulomatous disease (e.g. sarcoidosis)
 - Paget's disease of bone
 - Milk-alkali syndrome
 - Thiazide diuretics
 - Adrenal insufficiency
 - **Inappropriate Hypercalcemia:** (i.e. hypercalcemia with normal or raised PTH):
 - Primary hyperparathyroidism
 - Tertiary hyperparathyroidism
 - Lithium induced hyperparathyroidism
 - **Familial hypocalciuric hypercalcemia (FHH):**
 - It is an autosomal dominant condition.
 - It is due to mutation in calcium-sensing receptor in parathyroid & kidney.
 - It results in increased PTH secretion with consequent calcium retention in renal tubules (hypercalcemia).
 - It is almost always asymptomatic and without complications.
 - In contrast to primary hyperparathyroidism in which urinary calcium is high, FHH has low urinary calcium (Ratio of urinary Ca clearance to creatinine clearance is < 0.01).



Clinical Pearl:

Mechanisms for Hypercalcemia of Malignancy:

- Increased PTH-related Peptide (PTHrP):
 - Squamous cell cancers
 - Breast, bladder, & renal cancers
- Increased cytokines (increases osteoclastic activity) – hematologic malignancies
- Increased Calcitriol ($1, 25\text{-(OH)}_2\text{D}$) – lymphomas
- Local Osteolysis – breast cancer, multiple myeloma

▪ **Clinical Features:**

- Painful bones, renal stones, abdominal groans, and psychic moans.
(see above)
- Acute severe hypercalcemia:
 - Confusion
 - Constipation
 - Dehydration
 - Polyuria and polydipsia
 - **Short QT – interval on ECG**
 - Renal insufficiency, acute tubular necrosis

▪ **Diagnosis:**

- The best initial test is serum PTH:
 - Primary Hyperparathyroidism : high Ca, high PTH, low PO₄
 - Tertiary Hyperparathyroidism : high Ca, high PTH, high PO₄
 - FHH : high Ca, high PTH, low urinary Ca
 - Malignancy : high Ca, low PTH

▪ **Treatment:**

- Hydration: high-volume (3-4 liters) of normal saline
- Furosemide is given only AFTER hydration. (it increases calcium excretion by kidney)
- Bisphosphonate is very potent, but slow, taking a week to work.
- Calcitonin – if hydration and diuretic fail to control calcium levels then calcitonin works faster than bisphosphonates.
- Steroids – if the etiology is granulomatous (sarcoidosis)

II. Hypocalcemia:

- It refers to serum calcium level of < 8.5 mg/dL.

▪ **Causes:**

- Hypoparathyroidism
- Pseudo-hypoparathyroidism
- Vitamin D deficiency
- Hypo-magnesemia
- Chronic renal failure (secondary hyperparathyroidism)
- Calcium Sequestration:
 - Pancreatitis
 - Citrate excess (after blood transfusions)
 - Bisphosphonates

- Acute hyper-phosphatemia (acute renal failure, rhabdomyolysis, tumor lysis)

▪ Clinical Features:

- Perioral numbness
- Convulsions; psychosis
- Abdominal muscle cramps; Tetany
- **Chvostek's sign and Trousseau's sign**
- **Prolonged QT-interval**

▪ Treatment:

- Treat the underlying disorder.
- Acute Hypocalcemia:
 - Cardiac monitoring
 - IV 10% calcium gluconate (10 – 20 mL over 10 – 20 minutes), PLUS:
 - Calcitriol (vitamin D)+ Magnesium Chloride 50 – 100 mEq/day (if associated with hypomagnesemia)
- Chronic Hypocalcemia:
 - Oral calcium (1 – 3 g/day)
 - Oral vitamin D(ergocalciferol 50,000 IU x Once a week for 8 – 10 weeks)



Clinical Pearl:

Serum Calcium Level:

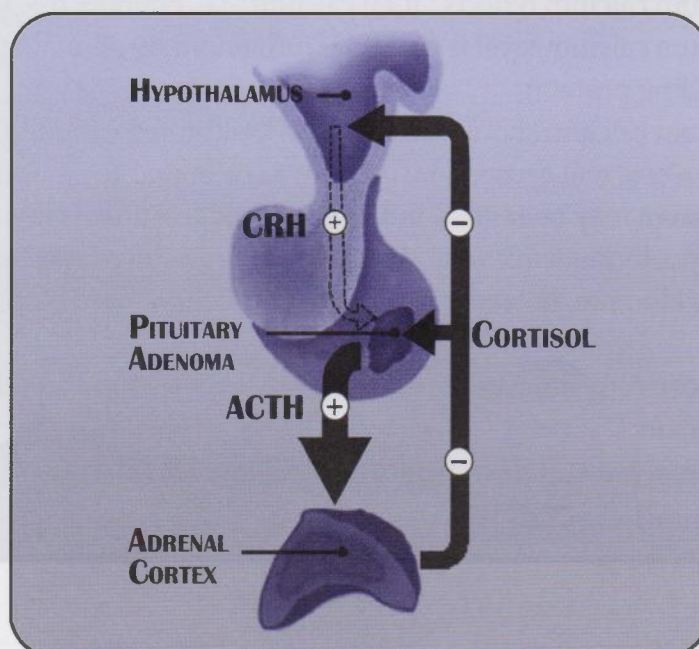
- Physiologically active calcium is **free (ionized) calcium**.
- Serum calcium reflects "**total calcium**" i.e. **bound + free (ionized) calcium**.
- Serum calcium level is therefore influenced by **albumin (main calcium-binding protein)**.
- Serum calcium should therefore be interpreted carefully, for example:
 1. Alkalosis will cause more calcium to be bound to albumin, therefore total calcium may be normal but free (ionized) calcium is low.
 2. Hypoalbuminemia (e.g. cirrhosis) may give increased total calcium due to low albumin, however free (ionized) calcium may be normal.
- To correctly interpret serum calcium level we need to calculate "**Corrected Calcium**".

Corrected Calcium (mg/dL) = measured calcium + {0.8 x (4 – albumin (gm/dL))}

Adrenal Disorders

Normal Physiology:

- The adrenal glands consist of cortex and medulla.
- The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines (i.e. epinephrine, nor-epinephrine).
- The adrenal cortex has three zones, responsible for the synthesis of three different types of steroids.
 - Zona glomerulosa = outermost zone; synthesizes mineralocorticoid (aldosterone)
 - Zona fasciculata = middle zone; synthesizes glucocorticoid (cortisol)
 - Zona reticularis = innermost zone; synthesizes sex steroids (estrogens & androgens)
- Hypothalamic-Pituitary-Adrenal Axis:
 - Corticotropin releasing hormone (CRH) is produced by hypothalamus.
 - CRH stimulates anterior pituitary to produce adrenocorticotropin hormone (ACTH)
 - ACTH acts on all zones of adrenal cortex increasing steroid hormone synthesis.
 - Cortisol inhibits the secretion of CRH from hypothalamus and secretion of ACTH from anterior pituitary in a negative-feedback pattern.
 - Aldosterone is under tonic control by ACTH, but is separately regulated by the renin-angiotensin system and by potassium.



Cushing's syndrome:

I. Introduction:

- It is a disorder caused by any condition that produces excessive glucocorticoids (cortisol).
- **Causes:**
 - Iatrogenic Cushing's syndrome (most common cause) – caused by exogenous administration of glucocorticoids.
 - Endogenous causes:
 - **Cushing's disease** (i.e. Cushing's syndrome secondary to pituitary tumor) – most common endogenous cause (60 – 70%)
 - Adrenal tumors – adrenal adenoma & adrenal carcinoma
 - Ectopic ACTH production:
 - Small cell lung cancer (most common)
 - Medullary thyroid cancer; carcinoid tumors

II. Clinical Features:

- Non-specific = secondary diabetes (gluconeogenesis); HTN; osteoporosis (bone resorption)
- More specific = central obesity with extremity wasting, moon facies.
- Most specific = spontaneous bruising, proximal myopathy, skin striae,
- Others = acne, hirsutism, depression, insomnia, susceptibility to infection
- Laboratory Findings:
 - Hyperglycemia
 - Hyponatremia
 - Hypokalemia (due to increased weak mineralocorticoid)
 - Metabolic alkalosis

III. Diagnosis:

- **Step 1: Does the patient have Cushing's syndrome?**
 - This step is to confirm Cushing's syndrome in a suspected case.
 - This step is carried out by performing ANY of the following three tests.
 - Dexamethasone Suppression Test
 - 24-Hour Urinary free Cortisol
 - Late-night Salivary Cortisol

(i). Dexamethasone Suppression Test:

Overnight Dexamethasone Suppression Test:

- It involves administration of 1 mg dexamethasone orally at 11:00 P.M. and then measuring serum cortisol level at 9:00 A.M.
- A normal person will suppress cortisol levels (< 50 nmol/L).
- Failure to suppress cortisol levels means the patient has Cushing's syndrome.

OR**48 – hour Low-dose Dexamethasone Suppression Test:**

- It involves administration of 0.5 mg dexamethasone 6-hourly for 48 hours; measuring 24 – hour urine cortisol during 2nd day.
- A normal person will suppress cortisol levels (< 50 nmol/L).
- Failure to suppress cortisol levels means the patient has Cushing's syndrome.

(ii). 24 – Hour Urinary Free Cortisol:

- ≥ 2 tests should be performed.
- It is positive if above the reference range for the assay.
 - Reference range for urinary free cortisol varies by age.
 - For individuals ≥ 18 years = $3.5 - 45$ $\mu\text{g}/24$ hour

(iii). Late – Night Salivary Cortisol:

- It involves measurement of salivary cortisol levels at 11 PM.
- It is positive if above the reference range.

**Clinical Pearl:****Suspected Cushing's syndrome:**

- If any of the above 3 tests are abnormal, repeat ≥ 1 of the above 3 tests.
- If repeat testing is normal then Cushing's is unlikely.
- If repeat testing is abnormal (≥ 2 concordant abnormal tests) confirm Cushing's syndrome.

- **Step 2: What is the cause of Cushing's syndrome?**

- The best next step after confirming Cushing's syndrome is the measure plasma ACTH level to determine the cause of Cushing's syndrome.
 - If plasma ACTH is low:
 - This means ACTH – independent Cushing's syndrome.
 - This means the source is in the adrenal gland.
 - The next step to confirm it is by doing CT scan (MRI) of the adrenals.
 - If plasma ACTH is normal or high:
 - This means ACTH – dependent Cushing's syndrome.
 - The source can be either:
 - Pituitary ACTH producing tumor
 - Ectopic ACTH production

- **Step 3: Differentiate between pituitary and ectopic ACTH production.**

- To differentiate between pituitary & ectopic source of ACTH perform ANY one of the following tests:
 - High-dose Dexamethasone Suppression Test – OR
 - Corticotrophin-Releasing Hormone (CRH) Test

48-hour High-dose Dexamethasone Suppression Test:

- It involves administration of 2 mg dexamethasone 6-hourly for 48 hours; measuring 24-hour urine cortisol at 0 (baseline) and 2nd day.
 - If high dose dexamethasone suppresses ACTH - the source is pituitary gland
 - If high dose fails to suppress ACTH - the source is ectopic.
- OR

Corticotrophin-Releasing Hormone (CRH) Stimulation Test:

- It involves administration of 100 mg of CRH IV, then measuring cortisol & ACTH.
- It is considered positive if > 20% rise of cortisol or 50% rise of ACTH.
- If high dose dexamethasone suppresses ACTH – OR
If CRH Stimulation Test is Positive:
 - The source is the pituitary gland.
 - The next step to confirm it is by doing MRI pituitary.
 - If MRI cannot detect the tumor (< 6 mm), the next step is “**Bilateral Inferior Petrosal Sinus venous Sampling (BIPSS)**” for ACTH measurement.
- If high dose dexamethasone fails to suppress ACTH – OR
If CRH Stimulation Test is Negative:
 - The source is ectopic ACTH production.
 - The next step to confirm it is by doing CT (MRI) Chest, CT (MRI) Abdomen to look for ectopic source (lung cancer, carcinoid).

IV.

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Treatment:

- Cushing's disease (pituitary tumor)
 - Trans-sphenoidal surgical removal of tumor.
 - If surgery not successful then:
 - Pituitary radiotherapy plus
 - Bilateral surgical adrenalectomy
- Adrenal tumors = surgical removal
- Ectopic ACTH producing-tumor = surgical removal
- Glucocorticoid replacement therapy after trans-sphenoidal surgery.
- Life-long glucocorticoid + mineralocorticoid replacement if adrenalectomy performed.

Origin of Cushing Syndrome

Lab test	Pituitary CS	Adrenal CS	Ectopic CS
Serum cortisol	Increased	Increased	Increased
24 – hour urinary cortisol	Increased	Increased	Increased
Low-dose dexamethasone	Cortisol not suppressed	Cortisol not suppressed	Cortisol not suppressed
Plasma ACTH	Increased	Decreased	Increased
High-dose dexamethasone	Cortisol “suppressed”	---	Cortisol not suppressed

Hyperaldosteronism:

- It is a small group of disorders characterized by excessive secretion of aldosterone (mineralocorticoid).
- It is broadly classified into three types:
 - Primary hyperaldosteronism
 - Secondary hyperaldosteronism – most common cause
 - Non-aldosterone dependent activation of mineralocorticoid pathway.

I. Primary Hyperaldosteronism:

- It refers to hyperaldosteronism associated with HIGH aldosterone and LOW renin.
- Causes:**
 - Aldosterone-secreting adenoma (**Conn Syndrome**)
 - Adrenocortical carcinoma
 - Adrenocortical hyperplasia
 - Glucocorticoid-remediable hyperaldosteronism.
- Diagnosis:**
 - Hypertension
 - Headache, muscle weakness
 - Polyuria, polydipsia; no peripheral edema
 - Hypernatremia (elevated serum sodium)
 - Hypokalemia
 - Metabolic alkalosis
 - Lab Findings:
 - Elevated aldosterone and decreased plasma renin.**
 - Plasma aldosterone: renin ratio > 20.**
 - Sodium suppression test** = fails to suppress aldosterone after sodium load.



Clinical Pearl:

Aldosterone: Renin Ratio (ARR):

- ARR is elevated in **primary** hyperaldosteronism.
- ARR can be altered by **anti-hypertensive** agents used for HTN in hyperaldosteronism.
 - Beta blockers inhibit renin activity and therefore increase ARR.
 - ACEI, ARBs, diuretics, stimulate renin activity and therefore decrease ARR.
- These agents should be stopped at least 2 weeks before testing.
- Alpha-blockers are best to control HTN during diagnostic testing.

II. Secondary Hyperaldosteronism:

- It refers to hyperaldosteronism associated with HIGH aldosterone and HIGH renin.
- Causes:
 - Renal artery stenosis
 - Congestive heart failure
 - Cirrhosis
 - Nephritic syndrome
 - Pregnancy (estrogen increases renin substrate)
 - Renin-secreting renal tumor
- Lab Findings:
 - **Elevated aldosterone,**
 - **Elevated plasma renin**

III. Non-aldosterone-dependent Activation of Mineralocorticoid:

- It refers to hyperaldosteronism associated with LOW aldosterone and LOW renin.
- Causes:
 - Ectopic ACTH syndrome
 - Licorice misuse
 - Liddle's syndrome (overexpressed distal tubular renal sodium channel)
 - 11-deoxycorticosterone-secreting adrenal tumor

IV.

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Treatment:

- Spironolactone:
 - It is aldosterone antagonist.
 - It treats both hypokalemia and hypertension.
 - Complications:
 - Hyperkalemia
 - Gynecomastia, which if develops switch to either:
 - Amiloride – OR
 - Eplerenone.
- Conn Syndrome:
 - Medical therapy (spironolactone) to normalize whole-body electrolyte balance.
 - Followed by surgical removal (ipsilateral adrenalectomy)

Adrenal Insufficiency:

- It results from inadequate secretion of cortisol and aldosterone.
- It is divided into two categories:
 - (i). Secondary Adrenal Insufficiency:**
 - It refers to decreased cortisol and/or aldosterone associated with **decreased ACTH.**
 - It is the most common cause of adrenal insufficiency.
 - It is caused by:
 - Rapid withdrawal of long-term glucocorticoid therapy – most common
 - Pituitary tumor
 - Hypothalamic disease

(ii). Primary Adrenal Insufficiency:

- It refers to decreased cortisol and/or aldosterone associated with **increased ACTH.**
- It is caused by:
 - Acute = Waterhouse-Friderichsen syndrome
 - Chronic = Addison's disease

I. Waterhouse-Friderichsen Syndrome:

- It refers to **acute, primary adrenocortical insufficiency** due to adrenal hemorrhage.
- It is a syndrome that mostly occurs in children.
- It is associated with:

- **Neisseria meningitidis septicemia**
- Hypotension leading to shock.
- DIC with widespread purpura

II. Addison Disease:

- It refers to **chronic, primary adrenocortical insufficiency**.
- **Causes:**
 - Tuberculosis (most common in developing countries).
 - Autoimmune adrenalitis (most common in developed countries).
 - AIDS
 - Metastatic cancers
 - Causes of Secondary adrenocortical insufficiency:
 - Cessation of long-term glucocorticoid treatment (most common)
 - Hypothalamic or pituitary disease
- **Symptoms:**
 - Weakness and fatigability
 - Orthostatic hypotension
 - Nausea, vomiting, diarrhea, anorexia, and weight loss
 - **Skin hyperpigmentation** (increased ACTH)
 - Electrolyte abnormalities:
 - Hyperkalemia
 - Hyponatremia
 - Metabolic acidosis
 - Hypoglycemia

Clinical Pearl:

Primary v/s Secondary Adrenal Insufficiency:

- In contrast to Addison's disease (primary adrenal insufficiency), secondary adrenal insufficiency is characterized by:
 1. Decreased pituitary ACTH production
 2. No skin hyperpigmentation
 3. No hyperkalemia

▪ **Diagnosis:**

Short ACTH-stimulation Test:

- It is also known as "Short Synacthen test".
- It involves administration of 250 µg ACTH by IM injection at any time of day.
- It is followed by taking blood samples for plasma cortisol (at 0 & 30 mins) & ACTH.
 - Normal = cortisol increase > 500 nmol/l (> 18 µg/dL)
 - Adrenal insufficiency = cortisol fails to increase (both primary & secondary)
 - Primary adrenal insufficiency will have High ACTH.
 - Secondary adrenal insufficiency will have Low ACTH.

▪ **Treatment:**

- Primary adrenal insufficiency:
 - Glucocorticoid = hydrocortisone (cortisol) is the drug of choice.
 - Mineralocorticoid = fludrocortisone
- Secondary adrenal insufficiency
 - Only glucocorticoid.
 - Mineralocorticoid is not given as it is not ACTH-dependent.

▪ **Adrenal (Adesonian) Crisis:**

- It refers severe episode of Addison's disease associated with:
 - Hypotension
 - Hyponatremia, hyperkalemia, hypoglycemia
 - Dehydration, pigmentation
 - Often with precipitating infection, trauma, or operation.



Treatment:

- IV resuscitation with normal saline – to normalize BP & pulse
- Intravenous hydrocortisone:
 - 100 mg IV stat, then:
 - 100 mg x 4 times daily for first 12 – 24 hours.
 - It should be continued until the patient is able to take oral therapy.
- If hypoglycemia – give IV 10% dextrose
- If severe hyponatremia (< 125 mmol/l):
 - Avoid increases of plasma Na > 10 mmol/l.
 - This is important to prevent pontine demyelination.
- Fludrocortisone is not required during acute treatment & can be introduced later.
- This is because high cortisol provides sufficient mineralocorticoid activity.

Pheochromocytoma:

- It is a neoplasm of chromaffin cells of adrenal medulla (80 – 90%), which synthesize and release catecholamines.
- It has rule of 10s.
 - 10% familial
 - 10% bilateral
 - 10% malignant
 - 10% in childhood
 - 10% extra-adrenal:
 - Organ of Zuckerkandl (aortic bifurcation)
 - Carotid body
 - Posterior mediastinum

- **Symptoms (5 P's):**

- Pressure = hypertension
- Pain = headache, chest pain
- Palpitations = tachycardia, tremors, weight loss, fever
- Perspiration = profuse sweating,
- Pallor

- **Diagnosis:**

- Increased plasma catecholamines (epinephrine, norepinephrine, dopamine)
- Increased urinary excretion of catecholamine metabolites:
 - Metanephrine = from epinephrine
 - Vanillylmandelic acid (VMA) = from norepinephrine
 - Homovanillic acid (HVA) = from dopamine
- Adrenal tumors = abdominal CT scan or MRI
- Extra-adrenal tumors = MIBG scintigraphy (meta-iodobenzyl guanidine)

- **Treatment:**

- Medical therapy (for 6 weeks), followed by surgery
- Preoperative volume expansion is critical due to possible hypotension after tumor resection.
- Medical therapy consists of:
 - Alpha blocker (**phenoxybenzamine** 10 – 20 mg PO x 3 times daily), followed by
 - Beta blocker (propranolol)



Clinical Pearl: Pheochromocytoma:

- Beta blockers must NEVER be given before **alpha-blocker** as this may cause a paradoxical rise in blood pressure due to unopposed α -mediated vasoconstriction.

Adrenogenital Syndromes:

- Also known as “Congenital Adrenal Hyperplasia (CAH)”.
- It is a group of autosomal recessive disorders.
- It is caused by deficiency of enzymes involved in the synthesis of cortisol and aldosterone.
- It is characterized by an enlargement of adrenal glands due to increased ACTH stimulation because of decreased cortisol.

	<u>Enzyme Deficiency</u>	<u>Features</u>
1	<u>21-hydroxylase deficiency (90%):</u> <ul style="list-style-type: none"> • Most common cause of (CAH) 	<p>Classic 21-OH Deficiency (Salt-wasting Syndrome)</p> <ul style="list-style-type: none"> ▪ Mineralocorticoids = decreased ▪ Cortisol = decreased ▪ Sex hormones (androgens) = increased. ▪ Clinical Features: <ul style="list-style-type: none"> ○ Hypotension; hyponatremia ○ Hyperkalemia; cardiovascular collapse <p>Non-classic 21-OH Deficiency:</p> <ul style="list-style-type: none"> ▪ Mineralocorticoids = normal ▪ Cortisol = decreased ▪ Sex hormones (androgens) = increased. ▪ Clinical Features: <ul style="list-style-type: none"> ○ Ambiguous genitalia in females (female pseudo-hermaphroditism) ○ Precocious puberty in males
2	<u>17-hydroxylase deficiency</u>	<ul style="list-style-type: none"> ▪ Mineralocorticoids = increased ▪ Cortisol = decreased ▪ Sex hormones (androgens) = decreased ▪ Clinical Features: <ul style="list-style-type: none"> ○ Hypertension; hypokalemia ○ XY Karyotype = male pseudo-hermaphroditism i.e. phenotypic female, but no internal reproductive organs, due to decreased dihydrotestosterone (DHT). ○ XX Karyotype = externally phenotypic female with normal internal sex organs, but lack secondary sexual characters.

	<u>Enzyme Deficiency</u>	<u>Features</u>
3	<u>11β-hydroxylase deficiency</u>	<ul style="list-style-type: none"> Mineralocorticoids = aldosterone decreased, but 11-deoxycorticosterone increased. Cortisol = decreased Sex hormones (androgens) = increased. Clinical Features: <ul style="list-style-type: none"> Hypertension (11 deoxycorticosterone) Masculinization
	<ul style="list-style-type: none"> Increased mineralocorticoids cause sodium retention with hypertension. Decreased mineralocorticoids cause sodium loss and hypotension. 	

I. Prolactinoma:

- It is the most common functioning pituitary adenoma.
- It is the most common pathologic cause of hyper-prolactinemia
- Hyper-prolactinemia (>390 mU/L) has following causes:

<u>Hyper-Prolactinemia</u>	
<p><u>Physiological:</u></p> <ul style="list-style-type: none"> Pregnancy Lactation Stress Drugs (most common cause): <ul style="list-style-type: none"> Dopamine antagonists (eg. metoclopramide) Antipsychotics Tramadol Methyldopa and reserpine 	
<p><u>Pathological:</u></p> <ul style="list-style-type: none"> Prolactinoma Hypothalamic disease Hypothyroidism (due to T_4) Chronic renal failure (excretion) 	

Clinical findings:

- Men:
 - Erectile dysfunction (impotence)
 - Loss of libido; decreased frequency of shaving
- Women:
 - Secondary amenorrhoea; infertility
 - Galactorrhoea

Pituitary Disorders

Hyperpituitarism:

- It refers to excess secretion of pituitary hormones.
- It is most commonly caused by pituitary adenomas of anterior lobe, such as:
 - Prolactinoma (most common)
 - Growth hormone adenoma
 - Thyrotroph adenoma
 - ACTH-producing adenoma
 - Gonadotroph adenoma

I. Prolactinoma:

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- Hyper-prolactinemia (> 390 mu/L) has following causes:

<u>Hyper-Prolactinemia</u>	
Physiological: <ul style="list-style-type: none"> ○ Pregnancy ○ Lactation ○ Sleep ○ Stress ○ Coitus 	Drugs: (most common cause): <ul style="list-style-type: none"> ○ Dopamine antagonist (e.g. metoclopramide) ○ Anti-psychotics ○ Estrogen ○ Methyldopa and reserpine
Pathologic: <ul style="list-style-type: none"> ○ Prolactinoma ○ Hypothalamic disease ○ Hypothyroidism (due to ↑ TRH) ○ Chronic renal failure (↓ excretion) 	

- Clinical findings:
 - Men:
 - Erectile dysfunction (impotence)
 - Loss of libido; decreased frequency of shaving
 - Women :
 - Secondary amenorrhea; infertility
 - Galactorrhea;



Clinical Pearl:

Prolactinoma:

- Prolactin is **ANTAGONIST** of GnRH and therefore decreases FSH & LH.
- Dopamine is the **ANTAGONIST** of prolactin.
- Prolactinoma can compress the optic chiasm.
- Optic chiasm compression results in **"bitemporal hemianopia"**

▪ Diagnosis:

- Always rule out pregnancy first in female patients.
- Always rule out hypothyroidism, because TRH can cause elevated prolactin levels.
- Serum prolactin level:
 - Normal level is < 500 mU/l.
 - $1000 - 5000$ mU/l is seen mostly in **microadenoma < 10 mm.**
 - > 5000 mU/l is seen mostly in **macroadenoma ≥ 10 mm**
 - The higher the level, the bigger the tumor.
- MRI of the pituitary gland.
- Visual field testing if MRI shows compression of optic chiasm.

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Treatment:

- Medical Management:
 - **Dopamine agonists are first-line therapy.**
 - Bromocriptine
 - Cabergoline
- Surgical Management:
 - Trans-sphenoidal surgery
 - It is performed when symptoms don't improve with medicines.
- Pregnancy:
 - Microadenoma = stop dopamine agonist therapy.
 - Macroadenoma:
 - Continue dopamine agonist therapy with monitoring of prolactin levels.
 - It is because macroadenoma may enlarge further during pregnancy under estrogen stimulation.

II. Growth Hormone Adenoma:

- Growth hormone adenoma is the second most common type of pituitary adenoma.
- Growth hormone has following functions:
 - Stimulates liver synthesis of insulin-like growth factor-1 (IGF-1).
 - Stimulates gluconeogenesis and amino acid uptake in muscle.
 - Stimulates linear and lateral growth of bone, cartilage, and soft tissue.
 - Negative feedback relationship with glucose and IGF-1.
- **Clinical Features:**
 - Gigantism:
 - It occurs when GH excess occurs **before closure of epiphysis**.
 - It therefore occurs in children.
 - Generalized increased in body size.
 - Disproportionately long arms and legs.
 - Acromegaly:
 - It occurs when GH excess occurs **after closure of epiphysis** (adults).
 - Headache & sweating – most common complaints
 - Prominent jaw (prognathism).
 - Frontal bossing and macroglossia.
 - Increased lateral bone growth.
 - Visual field defects.
 - Enlarged internal organs.
 - Thickened skin, myopathy
- **Diagnosis:**
 - Elevated serum GH and IGF-1
 - Elevated prolactin levels.
 - MRI brain to evaluate for tumor.
 - **Oral glucose tolerance test:**
 - Normally, serum GH suppresses to below 0.5 µg/L in response to glucose load.
 - In acromegaly GH fails to suppress (or paradoxically rise) in response to glucose.
 - It is a very sensitive test for acromegaly.
 - Screening for colon cancer with colonoscopy.
- **Complications:**
 - Heart failure from cardiomyopathy (**most common cause of death**)

- Diabetes mellitus (increased gluconeogenesis)
- Carpal tunnel syndrome
- Hypertension
- Colon cancer (2-3 times increased risk)

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Management:

- First line treatment = Surgery (trans-sphenoidal surgery)
- Second-line treatment (if disease persists after surgery):
 - Radiotherapy
 - Octreotide (somatostatin analogue that inhibits GH)
 - Pegvisomant (GH-receptor antagonist)
 - Bromocriptine (if elevated prolactin level)

Hypopituitarism:

I. Introduction:

- It refers to decreased secretion of pituitary hormones.
- It occurs when 75% of pituitary parenchyma is lost or absent.
- Causes:
 - Most common cause in adults = non-functioning adenoma.
 - Most common cause in children = craniopharyngioma.
 - Empty sella syndrome
 - Pituitary apoplexy
 - Sheehan syndrome
- Clinical Features:
 - Decreased GnRH = infertility, loss of libido and galactorrhea
 - Decreased GH = delayed growth (children), hypoglycemia (adults)
 - Decreased TSH = secondary hypothyroidism (already discussed)
 - Decreased ACTH = secondary adrenal insufficiency (already discussed)

II. Important Causes:

- Empty Sella Syndrome:
 - It refers to presence of empty sella turcica that is not filled with pituitary tissue.
 - It is classically seen in obese women with hypertension and multiple pregnancies.
- Pituitary Apoplexy:
 - It refers to sudden hemorrhage into pituitary gland, often occurring into a pituitary adenoma.

- It is a true neurosurgical emergency.
- Clinical Features:
 - Hypopituitarism
 - Severe headache
 - Diplopia (pressure on oculomotor nerve)
 - Cardiovascular collapse
 - Loss of consciousness
 - Sudden death

▪ **Sheehan Syndrome:**

- It refers to post-partum necrosis of anterior pituitary.
- Anterior pituitary enlarges during pregnancy, without increase in its blood supply.
- Anterior pituitary is therefore prone to ischemic necrosis due to obstetric hemorrhage.

▪ **Craniopharyngioma:**

- It is a hypothalamic suprasellar tumor.
- It is the most common cause of hypopituitarism in children.
- Features:
 - It is a benign tumor, derived from vestigial remnants of Rahtke's pouch.
 - It can undergo malignant transformation into squamous carcinoma (rare)
 - It may cause hyperpituitarism, or hypopituitarism, diabetes insipidus, or combination of these manifestations.

○ **Clinical Features:**

- Childhood:
 - Age 5 – 15 years.
 - It commonly presents with features of hypopituitarism.
- Adults:
 - Age > 50 years.
 - It commonly presents with visual disturbances.



Clinical Pearl:

Pituitary & Sellar Tumors:

- Most common intra-sellar tumors are pituitary macroadenoma.
- Most common supra-sellar tumors are craniopharyngioma.
- Most common para-sellar tumors are meningioma.

Posterior Pituitary Syndromes:

I. Diabetes Insipidus (DI):

- It is condition characterized by inability to produce concentrated urine due to ADH dysfunction.
- It is of two types:
 - Central Diabetes Insipidus (CDI)
 - Nephrogenic Diabetes Insipidus (NDI)
- **Central Diabetes Insipidus (CDI):**
 - It is due to deficiency of ADH
 - It may be caused by:
 - Head trauma
 - Tumors of hypothalamus
 - Inflammation of hypothalamus
 - Craniopharyngioma
 - **DIDMOAD:**
 - It is autosomal recessive disorder, also called "Wolfram's syndrome".
 - It stands for Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness.
- **Nephrogenic Diabetes Insipidus (NDI):**
 - It is due to unresponsiveness (resistance) of collecting tubules to ADH.
 - It may be caused by:
 - Lithium
 - Demeclocycline
 - Hypokalemia, hypercalcemia
 - Nephrocalcinosis
- **Diagnosis:**
 - CDI = ADH level is low,

- NDI = ADH level is high
- Decreased urine osmolality – excretion of large volumes of dilute urine.
- Increased serum osmolality
- Increased serum sodium (**hyponatremia**), which results in:
 - Excessive thirst and polydipsia
 - Neurologic features like confusion, disorientation, seizures (when hyponatremia is severe)

▪ **Water-deprivation Test:**

- Principle: to assess whether the kidneys still continue producing dilute urine despite dehydration, and then to localize the cause.
- The test can be divided into two stages:

(i). Stage – I: Water-deprivation for 8 Hours:

- Empty bladder, then no drinks and only dry food from 7:30 a.m.
- Monitor serum and urine osmolality, and weight every 2 hours for 8 hours.
- Stop the test if the patient loses > 3% weight.
- Stop the test after 8 hours (i.e. 15:30 p.m.)
- Interpretation:
 - Normal person:
 - Serum osmolality remains within normal range (275-295 mOsm/kg)
 - Urine osmolality rises to > 600 mOsm/kg.
 - Diabetes Insipidus:
 - **Serum osmolality rises to > 300 mOsm/kg**
 - **Urine osmolality fails to concentrate adequately i.e. < 600 mOsm/kg.**
 - Primary Polydipsia:
 - Serum osmolality is low at the start of the test.
 - Urine concentrates, but less than normal, e.g. > 400 – 600 mOsm/kg

(ii). Stage – II: Difference between CDI & NDI:

- Give desmopressin 2 µg IM if stage-I shows diabetes insipidus.
- If urine concentrates (> 600 mOsm/kg) after desmopressin = CDI.
- If urine doesn't concentrate after desmopressin = NDI.

R
X**Treatment:**

- CDI = Desmopressin (DDAVP):
 - It is an analogue of ADH with a longer half-life.
 - It is administered intra-nasally, but can be given orally or intramuscularly.
- NDI:
 - Correct potassium and calcium
 - Stop offending drugs
 - Thiazide diuretics (e.g. bendroflumethiazide or amiloride)
 - NSAIDs

II. Syndrome of Inappropriate ADH Secretion (SIADH):

- It is characterized by persistent ADH release independent of serum osmolality.
- It causes reabsorption of excess amounts of free water.
- **Causes:**
 - Small cell carcinoma of lung (most common)
 - Sarcoidosis
 - CNS injury
 - Tuberculosis
 - Drugs (anti-depressants, anti-psychotics)
- **Diagnosis:**
 - Increased urine osmolality (> 600 mOsm/kg)
 - Decreased serum osmolality (< 300 mOsm/kg)
 - Decreased serum sodium (**hyponatremia**).
 - Hyponatremia presents entirely with CNS symptoms:
 - Lethargy; confusion
 - Disorientation; seizures
- **Treatment:**
 - Fluid restriction – is the cornerstone of SIADH treatment.
 - Demeclocycline – ADH receptor antagonist.

Miscellaneous Conditions

I. Multiple Endocrine Neoplasias (MEN)

(i). MEN Type-I:

- Also known as Wermer syndrome.
- Inheritance = autosomal dominant
- Mutation = germline mutations in the "menin gene" located on chromosome 11.
- Characterized by (3Ps):
 - Pituitary adenomas (prolactinoma)
 - Primary hyperparathyroidism
 - Pancreatic islet tumors:
 - Gastrinoma – most common site is duodenum
 - Insulinoma
 - VIPoma
- Screening for MEN Type-I is mainly "biochemical" which starts at the age of 15 and consists of annual:
 - History taking and examination
 - Measurement of serum calcium, gastrointestinal hormones, and prolactin.
 - Intact serum PTH, fasting blood glucose
 - MRI of pituitary

(ii). MEN Type-IIA:

- Also known as Sipple syndrome.
- Inheritance = autosomal dominant.
- Mutation = germline mutations in the "RET proto-oncogene" located on chromosome 10.
- Characterized by:
 - Medullary thyroid carcinoma
 - Primary hyperparathyroidism
 - Pheochromocytoma

(iii). MEN Type-IIB:

- Inheritance = autosomal dominant.
- Mutation = germline mutations in the "RET proto-oncogene" located on chromosome 10.
- Characterized by:
 - Medullary carcinoma
 - Pheochromocytoma
 - Neuromas
 - Marfanoid habitus

- Screening for MEN Type-II is mainly “genetic” and consists of annual:
 - History taking and examination
 - Measurement of serum calcium and urinary catecholamine metabolites.
 - RET mutation testing.
 - Any patient having RET mutation should have prophylactic thyroidectomy early in childhood, because medullary thyroid cancer has 100% penetrance.

<u>MEN-IIIa</u>	<u>MEN-IIIb</u>
Medullary thyroid cancer	Medullary thyroid cancer
Pheochromocytoma	Pheochromocytoma
Hyperparathyroidism	Marfanoid habitus, neuromas

II. Autoimmune Polyendocrine Syndromes (APS):

(i). APS – I:

- Trait = Autosomal Recessive
- Mutation = Autoimmune Regulator Gene (AIRE) – (loss-of-function mutation)
- Also known as APECED i.e. Autoimmune Poly-Endocrinopathy-Candidiasis-Ectodermal Dysplasia.

(ii). APS – II:

- Most common type – also known as “Schmidt’s syndrome”.
- Trait = Autosomal Dominant with incomplete penetrance
- It is defined as presence of ≥ 2 autoimmune endocrine disorders in a patient.
- It typically presents in women aged 20 – 60 years.

<u>APS – I</u>	<u>APS – II</u>
Addison’s disease	Addison’s disease
Type-I DM	Type – I DM
Primary hypothyroidism	Primary hypothyroidism
Hypoparathyroidism	Primary hypogonadism
Chronic mucocutaneous candidiasis	Graves’ disease
Nail dystrophy	Celiac disease
Dental enamel hypoplasia	Pernicious anemia, Vitiligo, Myasthenia Gravis

III. Spontaneous Hypoglycemia:

(i). Introduction:

- In diabetics spontaneous hypoglycemia is most commonly caused as a side-effect of treatment with insulin or sulphonylurea drugs.
- In non-diabetics spontaneous hypoglycemia is diagnosed only when all conditions of "Whipple's triad" are met.

▪ Whipple's Triad:

- Patient has symptoms of hypoglycemia (e.g. odd behavior, convulsions)
- Low blood glucose measured at the time of symptoms
- Symptoms resolve on correction of hypoglycemia.

(ii). Differential Diagnosis:

- Whipple's triad, plus decreased insulin & decreased C-peptide:
 - Alcohol
 - Drugs
 - Critical illness (liver failure, renal failure)
 - Hypopituitarism
- Whipple's triad, plus increased insulin & decreased C-peptide:
 - Exogenous insulin
- Whipple's triad, plus increased insulin & increased C-peptide:
 - Insulinoma
 - Sulphonylurea
 - Hyperinsulinism of infancy

(iii). Management:

- Acute Hypoglycemia:
 - IV dextrose, followed with oral carbohydrate.
 - IM glucagon:
 - It stimulates hepatic glucose release.
 - It is however, ineffective when glycogen reserves are depleted (alcoholism, liver disease)
- Chronic recurrent hypoglycemia from insulin-secreting tumors:
 - Regular carbohydrate consumption plus;
 - Inhibitors of insulin secretion (e.g. diazoxide, thiazide diuretics, somatostatin analogue)
 - Insulinoma are usually resected.

IV. Polycystic Ovarian Syndrome (PCOS)

- It is the most common endocrine disorder in women.
- It is a syndrome of ovarian dysfunction along with the cardinal features of hyper-androgenism and polycystic ovary morphology.
- **Diagnostic Criteria (Rotterdam Criteria):**
 - The patient should have ≥ 2 of the following features:
 - Menstrual irregularity
 - Androgen excess – clinical or biochemical
 - Multiple cysts in the ovaries (detected by transvaginal US)
- **Clinical Features:**
 - Oligomenorrhoea/amenorrhea
 - Infertility
 - Hirsutism – (most common cause of hirsutism in female)
 - Obesity
 - Recurrent miscarriages
 - Acanthosis nigricans
 - Insulin Resistance:
 - Hyperlipidemia, Hypertension
 - Diabetes Mellitus type-II
- **Diagnosis:**
 - Elevated testosterone levels
 - Elevated 17-hydroxyprogesterone levels – **recommended screening test in suspected cases.**
 - Decreased sex-hormone binding globulin (SHBG)
 - **Elevated luteinizing hormone (LH) levels**
 - **Elevated LH: FSH ratio – LH is increased more than FSH $> 2.5: 1$.**
- **Treatment:**
 - Life-style Modifications:
 - It is the first-line management in patients with PCOS.
 - Weight loss & exercise – highly effective
 - Amenorrhea = weight loss, cyclical progesterone, metformin
 - Infertility = weight loss, clomiphene citrate (anti-estrogen), ovulation induction by gonadotropin therapy.
 - Obesity = weight loss, dietary modifications, metformin
 - Hirsutism:
 - Life cycle of hair follicle is 3 months.
 - Therefore, no improvement is likely before this time.

- Anti-Androgens:
 - Androgen Receptor Antagonists:
 - Cyproterone Acetate
 - Spironolactone, Flutamide
 - Finasteride (5-alpha-reductase inhibitor)
 - Combined oral contraceptive pills
- Eflornithine cream
- Permanent treatment:
 - Laser therapy
 - Electrolysis

V. Turner Syndrome:

- Also known as "Monosomy X".
- Incidence = 1: 2500 females.
- It is the most common cause of primary amenorrhea in women.
- **Karyotype = 45 XO**
- The genitals are female in character, although gonadal dysgenesis results in "streak ovaries".
- **Clinical Features:**
 - Primary amenorrhea
 - Primary infertility
 - Short stature
 - Webbed neck
 - Edema of hands and feet
 - Broad chest with wide-spaced nipples
 - Horse-shoe kidney
 - Coarctation of aorta
- **Diagnosis:**
 - FSH and LH = elevated
 - Karyotyping:
 - 45XO – most common
 - 45XO/ 46XY mosaicism
 - These patients are at increased risk of gonadoblastoma.
 - These patients should undergo prophylactic gonadectomy.
- **Treatment:**
 - Estrogen therapy can induce pubertal development.
 - Estrogen therapy, however, causes fusion of epiphysis and growth cessation – therefore timing of therapy should be carefully planned.

VI. Klinefelter Syndrome:

- Incidence = 1: 1000 males
- Karyotype = 47 XXY
- FSH & LH = elevated
- Pathogenesis:
 - Dysgenesis of the seminiferous tubules – principal abnormality
 - Leydig cell dysfunction – resulting in “hypergonadotrophic hypogonadism”.
- Clinical Features:
 - Tall stature,
 - Eunuchoid habitus
 - Gynecomastia
 - Small firm testes
 - Learning difficulties & behavioral disorders
 - Increased risk of:
 - Breast cancer
 - Type-II diabetes

Chapter 8

DIABETES MELLITUS



Diabetes Mellitus

Diabetes Mellitus Type – I:

- Also known as “Insulin-Dependent Diabetes Mellitus (IDDM).
- It is an autoimmune disorder characterized by absolute deficiency of insulin caused by β -cell destruction.
- **Pathogenesis:**
 - It is an autoimmune disease – the immune system mediates destruction of β -cells.
 - Overt diabetes develops when 80 – 90% of β -cells are lost.
 - Pathologic Feature:
 - The characteristic pathologic feature of type-I DM is “**Insulitis**”.
 - It is an early feature (pre-diabetes), presenting well before established diabetes.
 - It is characterized by infiltration of β -cells by mononuclear cells containing activated macrophages, B-cells, T-cells, and natural killer cells.
 - Insulitis is β -cell – specific as alpha-cells (glucagon) & delta cells (somatostatin) remain intact.
 - Islet Cell Antibodies:
 - These are present well before clinical presentation of diabetes.
 - Their detection can be useful confirming a diagnosis of type-I diabetes
 - They are poorly predictive of disease progression & disappear over time.
 - The most common islet cell antibodies are antibodies against glutamic acid decarboxylase (anti – GAD)
 - Anti-GAD antibodies may have a role in identifying late onset type-I DM in middle-aged people.



Clinical Pearl:

Increased Risk of Type-I DM:

- Positive family history
- HLA associations
- Anti-GAD antibodies
- Islet cell antibodies
- Autoimmune Diseases:
 - Thyroid disease, Pernicious Anemia
 - Celiac disease, Addison's disease, Vitiligo
 - Environmental Factors:
 - Infection with coxsackie virus B4, CMV, Rubella, EBV.
 - Dietary factors – nitrosamines (smoked & cured meats) & coffee
 - Bovine serum albumin (BSA) present in cow's milk.
 - Stress

Diabetes Mellitus Type – II:

- Also known as “Non-Insulin-Dependent Diabetes Mellitus (NIDDM).
- It is caused by combination of peripheral resistance to insulin and an inadequate secretory response by pancreatic β -cells.
- Pathogenesis:
 - Insulin Resistance:
 - DM type – II is associated with insulin resistance.
 - Insulin resistance is associated with constellation of features called “Syndrome X”, or “**Metabolic Syndrome**”, defined by International Diabetes Federation as:
 - Central obesity (defined as waist circumference with ethnicity-specific values), AND ≥ 2 of the following:
 - Hypertension ($\geq 130/85$ mmHg)
 - Triglycerides ≥ 150 mg/dL
 - HDL < 40 in men; < 50 in women
 - Fasting blood glucose > 100 mg/dL or already diagnosed type-II diabetes.
 - Pancreatic β -cell Failure:
 - At the time of diagnosis of type-II DM, 50% of β -cell function has been lost.
 - The characteristic pathologic feature of type-II DM is “**Amyloid Deposition**” in the Islets.

- β -cell number is reduced, but β -cell mass is unchanged.
- Glucagon secretion is increased, contributing to hyperglycemia.
- Environmental Factors:
 - Overeating
 - Physical inactivity
 - Aging – insulin decreases with age
 - Obesity:
 - **The risk of DM is increased tenfold in patients with BMI ≥ 30 kg/m².**
 - Obesity exacerbates insulin resistance.
 - It is associated with increased plasma levels of free fatty acids, which makes muscles more insulin resistant, reducing glucose uptake.
 - In the liver, free fatty acids increase the production of glucose.

<u>Type-1 Diabetes</u>	<u>Type-2 Diabetes</u>
<u>Onset:</u> <ul style="list-style-type: none"> ▪ Sudden 	<u>Onset:</u> <ul style="list-style-type: none"> ▪ Gradual
<u>Epidemiology:</u> <ul style="list-style-type: none"> ▪ Younger patients – usually < 30 years ▪ Body habitus – usually lean 	<u>Epidemiology:</u> <ul style="list-style-type: none"> ▪ Older patients – usually > 30 years. ▪ Body habitus – usually overweight
<u>Genetics:</u> <ul style="list-style-type: none"> ▪ Family history uncommon ▪ HLA DR3 and HLA DR4 association ▪ 30 – 50% concordance rate in identical twins 	<u>Genetics:</u> <ul style="list-style-type: none"> ▪ Family history common ▪ No HLA association. ▪ > 90% concordance rate in identical twins (much stronger genetic component than type-I)
<u>Features:</u> <ul style="list-style-type: none"> ▪ Ketosis – common ▪ Autoantibodies – present in most cases ▪ Endogenous insulin – decreased (absent) 	<u>Features:</u> <ul style="list-style-type: none"> ▪ Ketosis – rare ▪ Autoantibodies – absent ▪ Endogenous insulin – normal, increased, or decreased.

I. WHO Diagnostic Criteria:

Criteria 1:

- Symptomatic patients (i.e. polyuria, polydipsia, weight loss), PLUS
- Abnormal venous glucose on ONE occasion i.e.:
 - Fasting blood glucose ≥ 126 gm/dL (≥ 7 mmole/L), OR
 - Random blood glucose ≥ 200 gm/dL (>11.1 mmole/L),

Criteria 2:

- Asymptomatic patients, PLUS
- Abnormal venous glucose on TWO occasions i.e.:
 - Fasting blood glucose ≥ 126 gm/dL (≥ 7 mmole/L), OR
 - Random blood glucose ≥ 200 gm/dL (>11.1 mmole/L),

Criteria 3:

- HbA_{1C} of $\geq 6.5\%$
- It is a recently accepted criterion.

Oral Glucose Tolerance Test:

- It is required only for diagnosis of:
 - Borderline cases
 - Gestational diabetes

Oral Glucose Tolerance Test

Preparation Before Test:

- Unrestricted carbohydrate diet for 3 days.
- Overnight fasting for at least 8 hours.
- Sampling:
 - Plasma glucose is measured before and 2 hours after 75 g oral glucose drink

	<u>Normal</u>	<u>Impaired Glucose Tolerance</u>	<u>DM</u>
Fasting	< 7 mmol/L (< 126 mg/dL)	< 7 mmol/L (< 126 mg/dL)	≥ 7 mmol/L (≥ 126 mg/dL)
2 hours after glucose	< 7.8 mmol/L (< 140 mg/dL)	$7.8 - 11$ mmol/L ($140 - 199$ mg/dL)	> 11.1 mmol/L (≥ 200 mg/dL)

- Individuals with impaired glucose tolerance have increased risk of having DM.
- Individuals with impaired glucose tolerance advance to DM at rate of 5 – 10% per year.

II. Clinical Features:

- Polyuria – glucose in renal tubule causes osmotic retention of water, causing a diuresis
- Polydipsia – a physiologic response to diuresis to maintain plasma volume
- Fatigue
- Weight loss – from increased glycogenolysis, lipolysis, and gluconeogenesis
- Blurred vision – swelling of lens due to osmosis
- Numbness, tingling of hands and feet.
- **Type – I Diabetes:**
 - Symptoms develop quickly over days to weeks
 - Sometimes symptoms appear after an illness
 - **Diabetic Ketoacidosis:**
 - It is common in type – I DM, because:
 - There is absolute insulin deficiency which results in unrestrained lipolysis and proteolysis causing ketogenesis and weight loss.
 - When generation of ketone bodies exceeds their metabolism, ketoacidosis (DKA) results.
- **Type – II Diabetes:**
 - Hyperglycemia develops slowly and the renal threshold for glucose rises, so that osmotic symptoms are usually mild.
 - They have some insulin activity, required to suppress lipolysis and proteolysis, therefore weight loss and ketogenesis are not common.
 - **Hyperosmolar Non-ketotic Coma:**
 - Intercurrent illness (e.g. infection) increases the production of counter-regulatory hormones i.e. cortisol, growth hormone, and catecholamines.
 - This results in more severe hyperglycemia and dehydration (features of HONK)

Management:**I. Dietary Management:**

- Diet for people with diabetes should be:
 - Low in sugar
 - High in starchy carbohydrate (especially foods with low glycemic index)
 - High in fibre
 - Low in fat
- Following are some important dietary recommendations:
 - Protein = 1 g per kg ideal bodyweight

- Fat:
 - Total fat = < 35% of energy intake
 - Saturated and trans-unsaturated fat = < 10% of energy intake
- Carbohydrate:
 - Total carbohydrate = 40 – 60% of total energy intake
 - Avoid refined carbohydrate
- Vitamins:
 - Best taken as fruits and vegetables
 - There is no evidence for the use of supplements
- Salt:
 - Restrict to < 6 g per day.
 - Restrict to < 3 g per day if hypertensive.
- Alcohol:
 - It is not forbidden.
 - It can be consumed in moderation.
- Weight Reduction:
 - The risk of developing type-II diabetes increases 10 fold in people with a BMI of > 30 kg/m².
 - Therefore encourage patients to lose weight by:
 - Reduction in energy intake
 - Regular exercise for 30 minutes daily.

II. Oral Hypoglycemic Agents:

(i). Metformin:

- It is the only biguanide available; decreases HbA_{1C} by 1.5%
- Mechanism of action:
 - Increases insulin sensitivity
 - Increases peripheral glucose uptake
 - Impairs glucose absorption by the gut.
 - Inhibits hepatic gluconeogenesis.
- Indications for use:
 - It is first-line therapy for type-2 diabetes, irrespective of bodyweight.
 - It can be combined with insulin in obese patients with type-1 diabetes.
- Advantages:
 - No hypoglycemia
 - Weight loss
- Disadvantages:
 - GI upset (nausea, diarrhea, abdominal pain)
 - Lactic acidosis

- Contraindications:
 - Renal failure
 - Most clinicians withdraw the drug when serum creatinine is $> 150 \mu\text{mol/L}$ due to risk of lactic acidosis.

(ii). Sulphonylureas:

- These are insulin secretagogues i.e. stimulate pancreas to produce more insulin.
- These agents are valuable in the treatment of non-obese patients with type-2 diabetes who fail to respond to dietary measures alone. Decreases $\text{HbA}_{1\text{C}}$ by 1.5%.
- Agents:
 - First-generation = tolbutamide; chlorpropamide
 - Second-generation = glipizide; glibenclamide (only sulphonylurea that is safe in pregnancy)
- Features:
 - Advantages = effective and inexpensive
 - Disadvantages:
 - Hypoglycemia
 - Weight gain

(iii). Alpha-Glucosidase Inhibitors:

- These agents reduce glucose absorption from the gut, thereby reducing calorie intake.
- They are taken with each meal and lower post-prandial blood glucose.
- Agents: Acarbose; Miglitol
- Features:
 - Advantages = doesn't have significant toxicity
 - Disadvantages:
 - Diarrhea
 - Abdominal cramping; flatulence

(iv). Thiazolidinediones:

- They increase insulin sensitivity in adipose and skeletal muscle by binding to and activating peroxisome proliferator-activated receptor- γ (PPAR γ).
- Agents: Rosiglitazone; Pioglitazone
- Features:
 - Advantages
 - No increase in plasma insulin levels, therefore no hypoglycemia
 - Decreases $\text{HbA}_{1\text{C}}$ by 1%.

- Disadvantages:
 - Weight gain
 - Hepatotoxicity
 - Fluid retention and CHF
 - Bone fractures
 - Risk of MI with rosiglitazone, but not with pioglitazone
 - Contraindicated in patients with liver disease and heart disease (NYHA III-IV)

(v). DPP-4 Inhibitors (Gliptins):

- Glucagon-like peptide-1 (GLP-1) is a hormone, which stimulates insulin secretion.
- These agents inhibit dipeptidyl peptidase-4 (DPP-4), an enzyme which degrades GLP-1.
- Agents = sitagliptin; vildagliptin
- Advantages = no hypoglycemia; reduces appetite; weight loss

(vi). Exentide:

- It is a synthetic GLP-1 agonist; therefore increases insulin secretion.
- Advantages = weight loss
- Disadvantages:
 - Diarrhea
 - Pancreatitis

III. Insulin:

Method of administration:

- It is given intravenously for emergency ketoacidosis.
- Subcutaneous injections:
 - Needle sited at right angle to the skin.
 - Self-administered subcutaneously in abdomen, buttocks, arm, and leg.

Side-Effects:

- Hypoglycemia
- Weight gain
- Peripheral edema (from salt and water retention)
- Insulin antibodies (animal insulin)
- Local allergy
- Lipodystrophy at injection sites

▪ **Formulations:**

<u>Insulin</u>	<u>Formulation</u>	<u>Onset</u>	<u>Peak</u>	<u>Duration</u>
Rapid-acting	Lispro; Aspart	5 – 15 min	60 – 90 min	2 – 4 hours
Short-acting	Regular	30 – 60 min	2 – 4 hr	5 – 8 hours
Intermediate-acting	NPH, Lente	1 – 2 hours	4 – 8 hours	7 – 14 hours
Long-acting	Glargine, Ultralente	1 – 2 hours	None	18 – 24 hours

▪ **Regimens:**

- Most type-I diabetics require 0.5 – 1.0 unit/kg per day.
- Start with a conservative dose and adjust the regimen according to the patient's glucose controls.

Example 1:

- Twice – Daily Injections:
 - It usually involves injection of short acting insulin (Regular) + intermediate acting (NPH) in combination as 70/30 (i.e. 70% NPH and 30% Regular).
 - It is given before breakfast and the evening meal.
 - Two-thirds of total daily requirements of insulin is given in the morning; remaining one-third in the evening.

Example 2:

- Intensive Insulin Therapy:
 - It involves injection of long-acting insulin (Ultralente) once daily in the evening.
 - Regular insulin is given 30 – 45 minutes before each meal, and should be adjusted according to pre-prandial home glucose measurements.

▪ **Insulin Sliding Scale:**

- It is helpful in controlling blood glucose levels in the hospital setting.
- It involves injection of regular insulin, given according to bedside finger-stick glucose measurements.
- In general, sliding scale should be used in addition to a regimen of intermediate-acting insulin. If given alone, hyperglycemia usually results.
- Monitor blood glucose 4 times/day: before meals and at bedtime.
- Following approach can be used to adjust appropriate insulin doses:

- Take the total number of units of regular insulin that the patient required in 1 day (while on sliding scale).
- Add two-thirds of this the pre-breakfast dose and one-third before dinner.
- It should be given as 70/30.

Typical Insulin Sliding Scale (Regular Insulin)

<u>Blood glucose</u>	<u>Insulin Dose</u>
150 – 200	2 units
201 – 250	4 units
251 – 300	6 units
301 – 350	8 units
351 – 400	10 units



Clinical Pearl:

Dawn Phenomenon:

- It causes morning hyperglycemia.
- It is due to an increase in the nocturnal secretion of growth hormone.
- **Blood glucose level checked at 3 AM is elevated.**
- INCREASE the dose of evening insulin to provide additional coverage in the overnight hours.

Somogyi Effect:

- It causes morning hyperglycemia.
- It is a rebound response to nocturnal hypoglycemia – which activates counter-regulatory systems.
- **Blood glucose level checked at 3 AM is low.**
- DECREASE the dose of evening insulin to avoid nocturnal hypoglycemia

DKA & HHS

I. Diabetic Ketoacidosis (DKA):

- It is the hallmark of type-I diabetes.
- It is a medical emergency in which hyperglycemia is associated with metabolic acidosis due to greatly raised ketone levels.
- **Pathophysiology:**
 - It occurs in type-I DM, but may also occur in small number of ketosis-prone type-II DM.
 - It is characterized by:
 - Hyperglycemia (> 200 mg/dl [≥ 11 mmol/L])
 - Hyperketonemia (≥ 3 mmol/l) & ketonuria,
 - Increased anion-gap metabolic acidosis:
 - Venous pH < 7.3
 - Venous $\text{HCO}_3^- < 15$ mmol/l



Clinical Pearl:

Anion Gap:

- $\text{AG} = \text{Na} - [\text{Cl} + \text{HCO}_3^-]$
- $\text{AG} = 8 - 12$

- Hyperglycemia:
 - It is due to increased gluconeogenesis, increased glycogenolysis.
 - Decreased glucose uptake into cells.
 - It leads to osmotic diuresis, loss fluid and electrolytes, and dehydration.
- Ketoacidosis:
 - It is a state of uncontrolled catabolism associated with insulin deficiency.
 - It is due to:
 - Insulin deficiency causing mobilization and oxidation of fatty acids, increasing substrate for ketogenesis.
 - Decreased ketone clearance.
 - Accumulation of ketone bodies produces metabolic acidosis.
- **Precipitants (I's):**
 - Insulin deficiency (i.e. failure to take enough insulin)
 - Iatrogenic = glucocorticoids

- Infection = pneumonia, UTI
- Inflammation = pancreatitis, cholecystitis
- Ischemia & Infarction = myocardial infarction, gut ischemia, cerebral ischemia
- Intoxication = alcohol, drugs.

■ Clinical Features:

- Symptoms:
 - Polyuria, polydipsia, and dehydration.
 - Nausea, vomiting, and abdominal pain.
 - Weight loss, weakness, and blurred vision.
- Signs:
 - Tachycardia, hypotension
 - Dry mucous membranes (dehydration)
 - Cold extremities and peripheral cyanosis
 - Hypothermia
 - Kussmaul's breathing = deep breathing (air-hunger) to compensate metabolic acidosis with odor of acetone.
 - Apathy, drowsiness, confusion, and coma (10%).

■ Diagnosis:

- Blood glucose = elevated
- Ketosis = positive urine and serum ketones
- Urea, creatinine, electrolytes:
 - Increased BUN : Cr ratio (dehydration)
 - Serum sodium:
 - Pseudo-hyponatremia; therefore calculate corrected Na level.
 - $\text{Corrected Na} = \text{measured Na} + [2.4 \times (\text{measured glucose} - 100)/100]$.
 - Serum potassium:
 - **Total body potassium is LOW.**
 - But patient may initially have elevated plasma potassium (hyperkalemia) due to disproportionate water loss.
- Arterial blood gases (ABGs):
 - **Increased anion gap metabolic acidosis.**
 - $\text{Anion gap} = \text{Na} - (\text{Cl} + \text{HCO}_3)$, which normally is 8 – 12 mmol/L
 - Plasma bicarbonate level < 12 mmol/L indicates severe acidosis.
- CBC = leukocytosis (a stress response rather than infection)
- ECG



Treatment:

- Principles of management are:
 - Short-acting insulin
 - Fluid replacement
 - Potassium replacement
 - Antibiotics

(i). Insulin:

- Insulin is given by intravenous infusion.
- The blood glucose concentration should fall by 3 – 6 mmol/L (55 – 110 mg/dL) per hour.
- Aggressive fall of blood glucose can lead to hypoglycemia & cerebral edema.
- The blood glucose concentration should be checked every hour.
- Half-life of IV insulin is short (2.5 min), therefore the infusion should not be interrupted.
- Insulin sliding scales should not be used.
- Regimen:
 - 10 U bolus of IV insulin, followed by 0.1 U/kg/hour.
 - Continue insulin drip until anion gap is normal.
 - Once anion gap is normal shift to subcutaneous insulin.
 - Continue IV insulin for at least 30 minutes after starting SC insulin – to prevent rebound ketoacidosis

(ii). Fluid Replacement:

- Extracellular fluid loss is replaced by normal saline.
- Intracellular fluid loss is replaced by dextrose.
- Normal Saline:
 - Start NS at 10 – 14 ml/kg/hour.
 - Tailor infusion to hydration and cardiovascular status.
 - Regimen:
 - 1 – 3 L = First hour
 - 1 L = Over following 1 hour
 - 1 L = Over following 2 hours
 - 1 L = Over following 4 hours

(Again, rate of replacement depends on degree of dehydration & cardiovascular status [CVP])

- Dextrose:
 - Start 10% dextrose when blood glucose < 250 mg/dL (< 14 mmol/l).
 - Start 10% dextrose at 125 ml/hour IV.



Clinical Pearl:

DKA:

- The main objective of treatment is to normalize the anion gap.
- Therefore, even if blood glucose falls, but AG remains elevated, insulin therapy should continue, but don't forget to add 10% dextrose.
- Once the anion gap is normalized you can start SC insulin.
- However, continue IV insulin (with SC insulin) for at least 30 minutes to prevent rebound ketoacidosis.
- Start K replacement once serum K is < 5.5

(iii). Potassium Replacement:

- Remember: in DKA patient may have hyperkalemia, but total body potassium is low.
- K monitoring & replacement is an essential part of DKA management.
- K monitoring should take place hourly.
- Regimen:
 - If serum K is > 5.5 = no replacement
 - If serum K is < 5.5 :
 - Start potassium replacement
 - Add 20 – 40 mEq/L of KCl to each liter of fluid once K is < 5.5
 - If serum K is < 3.5 :
 - Ask senior help.
 - It is advisable not to start IV insulin, unless K replacement is underway.
 - It is because insulin promotes entry of K into cells.
 - This aggravates hypokalemia, with risk of life-threatening arrhythmias.

(iv). Additional Features:

- Antibiotics for infection
- Sodium bicarbonate infusion in severe acidosis ($\text{pH} < 7.0$) or cardiac instability.
- Catheterization if no urine passed after 3 hours.
- DVT prophylaxis with low molecular weight heparin.
- Phosphate replacement if < 1 mmol/l.
- Plasma expander if systolic BP is < 90 mmHg.

II. Hyperosmolar Hyperglycemic State (HHS):

- It is a metabolic emergency characteristic of uncontrolled type-II diabetes.
- It is characterized by severe hyperglycemia without significant ketoacidosis.
- It was previously referred to as "Hyperosmolar Non-Ketotic (HONK) coma, but coma is not a common feature.
- **Clinical Features:**
 - Dehydration, stupor, or coma.
 - Precipitating factors are same as that for DKA, but also include dehydration & renal failure.
 - Diagnosis:
 - Hyperglycemia (usually > 600 mg/dL)
 - Increased serum osmolality > 320 mOsm/L.
 - Altered mental status
 - Profound dehydration (up to an average of 9 L)
 - No ketoacidosis (< 3 mmol/L)
 - Raised BUN: Cr ratio



Clinical Pearl:

Poor Prognostic Signs in HHS:

- Hypothermia
- Hypotension (SBP < 90 mmHg)
- Tachycardia, Bradycardia
- Severe hypernatremia (Na > 160 mmol/L)
- Serum osmolality > 360 mOsm/kg
- Presence of other serious comorbidities



Treatment:

○ Fluid Replacement:

- Calculate & measure serum osmolality regularly:

Plasma Osmolarity = $2 [\text{Na}] + [\text{Glucose (mmol/l)}] + [\text{Urea (mmol/l)}]$

Plasma Osmolarity = $2 [\text{Na}] + [\text{Glucose/18 (mg/dl)}] + [\text{BUN/2.8 (mg/dl)}]$

Plasma Osmolarity = 280 – 290 mmol/L

- Aggressive hydration is the best initial management in patients with HHS.
- 0.9% normal saline (NS) is the best initial fluid choice.
- 0.45% NS is started only if osmolality is increasing, despite positive fluid balance.
- Target fall in plasma Na is ≤ 10 mmol/L at 24 hours.

○ Insulin Therapy:

- Many patients with HHS responds to fluid resuscitation alone.
- However, insulin therapy can be used to facilitate correction of hyperglycemia.
- Monitor blood glucose hourly.
- Start insulin when blood glucose is not falling with 0.9% NS.
- Start IV insulin at 0.05 – 0.1 U/kg/hour.
- Reduce blood glucose by no more than 5 mmol/L/hour (90 mg/dL/hour)
- Aggressive blood glucose reduction results in cerebral edema.



Clinical Pearl:

HHS & Insulin Therapy:

- Best initial therapy for HHS is fluid resuscitation.
- Insulin is contraindicated in the initial management of patients with HHS.
- The osmotic pressure of glucose within the vascular space contributes to the maintenance of circulating volume in these severely dehydrated patients.
- Insulin therapy drives glucose, potassium, and water into cells. This results in circulatory collapse if fluid has not been replaced first.

- Additional Measures:
 - Treat coexisting conditions.
 - DVT prophylaxis with subcutaneous low molecular weight heparin.
 - Start potassium replacement once serum K is < 5.5 mmol/l.
 - Provide adequate nutritional support for all patients.

III. Lactic Acidosis:

Clinical Features:

- Very ill and over-breathing patient.
- Coma
- Patient is likely to be taking metformin for type-II diabetes.
- Patient's breath doesn't smell of acetone.

Diagnosis:

- Increased anion gap metabolic acidosis.
- No significant hyperglycemia
- No significant ketosis
- Diagnosis confirmed by a high concentration of lactic acid in the blood.

Treatment:

- Intravenous sodium bicarbonate
- Insulin and glucose
- Mortality is 50%.

Long-term Complications of Diabetes

Diabetic Retinopathy:

- It is a common cause of blindness in adults.
- Pathogenesis:
 - Hyperglycemia increases retinal blood flow and metabolism, and has direct effects on retinal endothelial cells, resulting in impaired vascular auto-regulation.
 - This leads to chronic retinal hypoxia which stimulates production of growth factors causing new vessel formation and increased vascular permeability.

I. Classification:

▪ Background Retinopathy:

- It is also known as non-proliferative retinopathy.
- It is characterized by:
 - Dot hemorrhages (capillary micro-aneurysms) appear first.
 - Blot hemorrhages i.e. leakage of blood into deeper retinal layers
 - Hard exudates (i.e. exudation of plasma rich in lipids and proteins)
- Action needed:
 - No immediate threat to vision
 - Annual ophthalmologic screening only
 - Control blood glucose, lipids, blood pressure; stop smoking

▪ Pre – Proliferative Retinopathy:

- It is characterized by:
 - Venous beading and venous loops
 - Cotton wool spots (represent arteriolar occlusions causing retinal ischemia)
 - Intra-retinal microvascular abnormalities (IRMAs):
 - These are features of severe pre-proliferative retinopathy.
 - These are dilated, tortuous capillaries representing patent capillaries in an area where most have been occluded.
- Action needed:
 - Sight-threatening
 - Non-urgent referral to an ophthalmologist.

▪ **Proliferative Retinopathy:**

- It is characterized by:
 - Neovascularization i.e. new blood vessel formation
 - Rubeosis iridis i.e. new blood vessel formation on the anterior surface of iris
 - Pre-retinal hemorrhage
 - Vitreous hemorrhage
- Action needed:
 - Sight threatening
 - Urgent referral to an ophthalmologist

▪ **Maculopathy:**

- It is characterized by:
 - Hard exudates within one disc-width of macula
 - Macular hemorrhage, ischemia, and edema
- Action needed:
 - Sight-threatening
 - Refer to an ophthalmologist

II.

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Management:

▪ **Prevention:**

- Regular (annual) screening for retinopathy is essential in all diabetic patients.
- Strict glycemic control reduces the risk of retinopathy.
- Smoking and HTN worsen the rate of progression.
- Blood pressure control is of great importance.
- Glycemic control should be gradual, as sudden lowering of blood glucose may worsen retinopathy by causing relative ischemia.

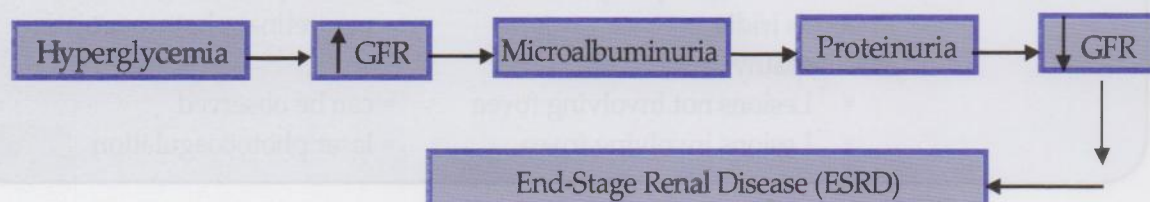
▪ **Treatment:**

- | | |
|-------------------------------|--------------------------------|
| ○ Background retinopathy | = no specific treatment |
| ○ Proliferative retinopathy | = retinal photocoagulation |
| ○ Rubeosis iridis | = pan-retinal photocoagulation |
| ○ Maculopathy: | |
| ▪ Lesions not involving fovea | = can be observed |
| ▪ Lesions involving fovea | = laser photocoagulation |

Diabetic Nephropathy:

I. Introduction:

- It is among the most common causes of end-stage renal disease (ESRD).
- **Definition:**
 - Persistent macroalbuminuria (> 300 mg/day) (confirmed on at least 2 occasions 3 – 6 months apart)
 - Progressive decline in glomerular filtration rate (GFR)
 - Elevated arterial blood pressure
- **Risk Factors:**
 - Poor glycemic control
 - Long duration of diabetes
 - Asian ethnicity
 - Pre-existing HTN
 - Family history of HTN
 - Family history of diabetic nephropathy
- **Pathophysiology:**
 - It is characterized by 3 major histopathologic changes (induced by hyperglycemia):
 - Mesangial expansion – due to increased extracellular matrix
 - Glomerular basement membrane (GBM) thickening
 - Glomerular Sclerosis – due to intra-glomerular HTN.
 - Diffuse glomerulosclerosis – diffuse glomerular hyaline deposition
 - Nodular glomerulosclerosis (**Kimmel-Wilson Nodules**) – hyaline deposition in ONE area of glomerulus
 - Kimmel-Wilson nodules are pathognomonic of diabetic nephropathy.
 - Natural History of Diabetic Nephropathy:



II. Diagnosis & Screening:

- Micro-albuminuria:
 - Definitions:
 - 24-hour urine collection = excretion of 30 – 300 mg albumin per day.
 - Urine albumin – creatinine ratio (ACR):
 - Men = 2.5 – 30 mg/mmol
 - Women = 3.5 – 30 mg/mmol
 - It is an important indicator of the risk of developing overt diabetic nephropathy.
 - It is also a strong independent risk factor for cardiovascular disease in type-2 diabetes
- Who to screen:
 - Type – I diabetes = annually from 5 years after diagnosis
 - Type – II diabetes = annually from the time of diagnosis

II.**R_x****Management:**

- Strict glycemic control
- Strict blood pressure control:
 - Hypertension increases the risk of progression of diabetic nephropathy to ESRD.
 - Target BP $\leq 130/80$ (the lower the better)
 - ACEI or ARBs have shown to slow the progression of diabetic nephropathy.
 - ACEI/ARBs + statins + aspirin in type-II patients with micro-albuminuria have reduced the risk of CV disease, nephropathy, and retinopathy.
- Anti-diabetic drugs:
 - Diabetic control becomes difficult as renal impairment progresses.
 - Treatment with metformin should be withdrawn when creatinine is $> 150 \mu\text{mol/L}$ (1.7 mg/dL), as the risk of lactic acidosis is increased.
- Other Measures:
 - Low-protein diet
 - Dialysis
 - Transplantation:
 - Renal transplantation dramatically improves patient's life.
 - Associated microvascular & macrovascular disease elsewhere may still progress.
 - Combined pancreatic transplantation produces insulin independence.
 - Combined pancreatic transplantation can delay or reverse microvascular disease.

Diabetic Neuropathy:

- It affects approximately 30% of diabetic patients.
- It can occur in motor, sensory, and autonomic nerves.
- It can be classified as follows:
 - Autonomic neuropathy
 - Somatic neuropathy:
 - Mononeuropathy
 - Polyneuropathy:
 - Symmetrical polyneuropathy – mainly sensory & distal
 - Asymmetrical polyneuropathy – mainly motor & proximal

I. Somatic Neuropathy:

- **Symmetrical Sensory Polyneuropathy:**
 - Symptoms:
 - Asymptomatic
 - Paraesthesias in the feet
 - Pain in the lower limbs – worse at night, mainly on anterior aspect of legs
 - Burning sensations in the soles of feet; cutaneous hyperesthesia
 - Abnormal gait – commonly wide-based
 - Muscle weakness and wasting in advanced cases
 - Signs:
 - Diminished perception of vibration sensation distally
 - “Glove-and-Stocking” impairment of all other modalities of sensation
 - Loss of tendon reflexes in the lower limbs
 - Clawing of toes with wasting of interosseous muscles.
 - Management:
 - Strict glycemic control
 - Tricyclic antidepressants (amitriptyline, imipramine), anti-convulsant (gabapentin), and opioids (tramadol, oxycodone)
- **Asymmetrical Motor Polyneuropathy:**
 - Also known as “Diabetic Amyotrophy”.
 - It is thought to involve acute infarction of lumbosacral plexus.
 - Clinical Features:
 - Severe and progressive weakness and wasting of proximal muscles
 - Lower limb > upper limb
 - Associated with severe pain, hyperesthesia, and paraesthesias.

- Associated with marked loss of weight ("Neuropathic Cachexia")
- Signs:
 - Absent tendon reflexes on affected side
 - CSF protein is raised.
- Management:
 - Recovery occurs within 12 months; some deficits become permanent
 - Treatment is mainly supportive.
- **Mononeuropathy:**
 - Mononeuropathy refers to involvement of a single peripheral or cranial nerve.
 - Mononeuritis multiplex refers to multiple mononeuropathies.
 - Features:
 - Mononeuropathies are severe and of rapid onset; but eventually recover.
 - Most commonly affected nerves are:
 - 3rd and 6th cranial nerves – resulting in diplopia
 - Femoral and sciatic nerves
 - Nerve compression palsies affect:
 - Median nerve (most common) – presenting as carpal tunnel syndrome
 - Lateral popliteal nerve – resulting in foot drop

II. Autonomic Neuropathy:

- It refers to involvement of parasympathetic or sympathetic nerves in ≥ 1 visceral system.
- **Clinical Features:**
 - Cardiovascular System:
 - Resting tachycardia
 - Fixed heart rate
 - Postural hypotension i.e. a drop in systolic pressure of ≥ 30 mmHg on standing from the supine position
 - Gastrointestinal System:
 - Dysphagia – due to esophageal atony
 - Diarrhea
 - Constipation – due to colonic atony
 - Gastroparesis:
 - It is due to delayed gastric emptying.
 - It presents with abdominal fullness, nausea and vomiting.

- Genitourinary:
 - Atonic bladder (urinary incontinence, recurrent infection)
 - Erectile dysfunction
- Pupillary:
 - Decreased pupil size
 - Delayed or absent reflexes to light
- Sudomotor:
 - Hyperhidrosis i.e. excessive sweating
 - Anhidrosis

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Management:

<u>Management of Autonomic Neuropathy</u>	
<u>Feature</u>	<u>Management</u>
Gastroparesis	Metoclopramide (dopamine antagonist); Erythromycin
Diarrhea	Loperamide, clonidine, Octreotide
Constipation	Stimulant laxatives
Atonic bladder	Intermittent self-catheterization
Hyperhidrosis	Anti-cholinergics (propantheline) Anti-muscarinic (glycopyrrolate cream)
Erectile dysfunction	<ul style="list-style-type: none"> ▪ Phosphodiesterase-5 inhibitors (sildenafil) ▪ Dopamine agonist (apomorphine) ▪ Prostaglandin E injections ▪ Implantable penile prosthesis
Postural hypotension	<ul style="list-style-type: none"> ▪ Supportive stockings ▪ Fludrocortisone ▪ Alpha-adrenoceptor agonist (midodrine) ▪ NSAIDs

Clinical Pearl:

Macrovascular Complications of Diabetes:

- The main problem is accelerated atherosclerosis.
- This puts the patient at increased risk of CAD, stroke, and CHF.
- CAD is the most common cause of death in diabetic patients.
- Target BP $\leq 130/80$
- Target LDL < 100
- Target HDL > 40



Clinical Pearl:

Microvascular Complications of Diabetes:

- This includes nephropathy, retinopathy, & neuropathy.
- Effect of strict glycemic control:
 - Macrovascular complications = none
 - Retinopathy & nephropathy = decreases progression
 - Neuropathy = decreases onset as well as progression

Gestational Diabetes:

- It is defined as diabetes with first onset or recognition during pregnancy.
- Risk Factors:
 - BMI > 30 kg/m²
 - Previous macrosomic baby weighing ≥ 4.5 kg at birth
 - Previous gestational diabetes
 - A first-degree relative with diabetes
 - High-risk ethnicity – South Asian, Middle Eastern, Black Caribbean
- Oral Glucose Tolerance Test:
 - It should be performed in all patients with high-risks (above)
 - It is performed between 24 – 28 weeks of gestation.
 - Measure 75-g oral glucose tolerance test in the morning after an overnight fast of at least 8 hours.
- Diagnosis of GDM:
 - Fasting glucose ≥ 95 mg/dL
 - 1 hour plasma glucose - > 190 mg/dL
 - 2

Diagnostic: Measure 100-g OGTT in all women to be tested at 24–28 weeks

- May be preferred in clinics with high prevalence of GDM
- Should be performed in the morning after an overnight fast of at least 8 h
- Diagnosis of GDM if at least two of the following plasma glucose values are found:
 - Fasting: ≥95 mg/dL
 - 1 h: ≥180 mg/dL post oral glucose
 - 2 h: ≥155 mg/dL post oral glucose
 - 3 h: ≥140 mg/dL post oral glucose

Chapter 9

GASTROENTEROLOGY



Esophageal Disorders

Dysphagia:

- "Dysphagia" refers to difficulty swallowing.
- "Odynophagia" refers to pain on swallowing.
- Dysphagia is of two types:

I. Oropharyngeal Dysphagia:

- It is dysphagia characterized by:
 - Difficulty "initiating" swallowing movement.
 - It is associated with choking or aspiration of food into the lungs or nasal regurgitation.
 - **It is more for liquids than for solids.**
 - Diagnosis = video fluoroscopy.
 - Causes:
 - Neurological:
 - Bulbar palsy
 - Pseudobulbar palsy
 - Myasthenia gravis
 - Stroke
 - Structural:
 - Oral cancer
 - Zenker's diverticulum.

II. Esophageal Dysphagia:

- It is dysphagia characterized by:
 - "Sticking sensation" of food after swallowing.
 - Obstructive lesions cause dysphagia **for solids more than liquids.**
 - Obstructive lesions are diagnosed by endoscopy and biopsy.
 - Motility disorders cause dysphagia **for both solids and liquids.**
 - Motility disorders are diagnosed by manometry and barium swallow.

- Esophageal dysphagia + odynophagia = esophagitis
- Causes:
 - Obstruction:
 - Strictures; esophageal webs
 - Schatzki rings; Esophageal carcinoma
 - Motility disorders:
 - Achalasia
 - Diffuse esophageal spasm

Esophageal Motility Disorders:

I. Achalasia:

Definition:

- It is esophageal motility disorder with 3 major abnormalities:
 - Failure of lower esophageal sphincter (LES) to relax with swallowing
 - Aperistalsis (loss of peristalsis) in the distal two-thirds,
 - Increased resting tone of LES

Pathogenesis:

- It results from degeneration of inhibitory neurons in the myenteric (Auerbach's plexus)
- Inhibitory neurons contain nitric oxide and vasoactive intestinal peptide (VIP) in distal esophagus.
 - Loss of ganglion cells in myenteric plexus = loss of smooth muscle motility
 - Loss of nitric oxide = incomplete relaxation of LES.

Causes:

- Idiopathic
- Chagas disease
- Diabetic autonomic neuropathy
- Amyloidosis
- Sarcoidosis
- Pseudo-achalasia = achalasia like symptoms due to cancer of gastro-esophageal junction.

Clinical Presentation:

- Dysphagia (difficulty swallowing)
- Dysphagia is both for solids and liquids.
- Age is mostly < 50 years.

- Weight loss
- Nocturnal cough, regurgitation
- Heartburn does NOT occur because the closed esophageal sphincter prevents reflux.

▪ **Diagnosis:**

- Barium Swallow:
 - **Bird's beak appearance i.e.:**
 - Esophageal dilatation with uniform tapering of distal esophagus.
- Esophageal Manometry (confirms diagnosis):
 - Increased resting pressure in LES
 - Decreased peristalsis in the body of esophagus.

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Treatment:

- Pharmacologic:
 - Calcium channel blockers; Nitrates
 - Endoscopic injection of botulinum toxin into the LES.
- Non-pharmacologic:
 - Pneumatic dilatation
 - Surgical = Heller's myotomy

Clinical Pearl:

Dysphagia & Motility Disorders:

- Dysphagia caused by **Scleroderma** has following manometric features:
 - Peristalsis = decreased
 - Resting LES pressure = decreased
- Dysphagia caused by **Achalasia** has following manometric features:
 - Peristalsis = decreased
 - Resting LES pressure = increased.

▪ **Complications:**

- Squamous cell carcinoma 5% (most serious)
- Candida esophagitis
- Diverticulitis
- Aspiration pneumonia
- Airway obstruction

II. Diffuse Esophageal Spasm & Nutcracker Esophagus:

- It is a motility disorder in which normal peristalsis is periodically interrupted by high-amplitude **non-peristaltic contractions**.
- Clinical Features:
 - Episodic chest pain, mimicking an angina.
 - Transient dysphagia.
- Diagnosis:
 - Barium swallow = "**Corkscrew**" appearance due to dyscoordinated diffuse contractions.
 - Manometry = repetitive high-amplitude contraction (400 – 500 mmHg)
- **Nutcracker Esophagus:**
 - It is a condition in which extremely forceful peristaltic activity leads to episodic chest pain and dysphagia.
 - Manometry = very strong **peristaltic waves** of > 180 mmHg.

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Treatment:

- Calcium channel blockers
- Nitrates
- Pneumatic dilatation
- Surgical myotomy

III. Zenker diverticulum (Pharyngeal Pouch):

- Also known as pharyngoesophageal diverticulum.
- It is the most common esophageal diverticulum.
- It is defined as outpouching through the cricopharyngeus muscle, above the upper esophageal sphincter.
- It protrudes through the natural weak point i.e. **Killian's Dehiscence** between inferior pharyngeal constrictor and cricopharyngeus muscle.
- **Clinical Features:**
 - Dysphagia, regurgitation,
 - Mass in the neck.
 - Halitosis – due to entrapped food
 - When diverticulum is small = pharyngeal dysphagia
 - When diverticulum is large = esophageal dysphagia
- **Management:**
 - Diagnosis:
 - Barium swallow will demonstrate outpouchings.
 - Endoscopy may be hazardous; as it can perforate the pouch.

- Treatment:

- Surgery is the treatment of choice in symptomatic patients.
- It involves myotomy and resection of the pouch.

Esophageal Infections & Inflammations:

I. Gastroesophageal Reflux Disease (GERD):

- Also known as “reflux esophagitis”.
- It refers to reflux of gastric contents into the lower esophagus, resulting in esophageal irritation and inflammation.
- **Pathogenesis:**
 - Transient LES relaxation, OR
 - Incompetent LES.
- **Risk factors:**
 - Sliding hiatal hernia
 - Delayed gastric emptying
 - Reduction in reparative capacity of mucosa
 - Decreased LES tone due to:
 - Hypothyroidism
 - CNS depressants
 - Pregnancy
 - Alcohol
 - Tobacco
- **Clinical features:**
 - Esophageal:
 - Heartburn and regurgitation are the major symptoms.
 - Heartburn is provoked by bending, straining, or lying down.
 - Dysphagia,
 - “**Water brash**” – salivation due to reflex salivary gland stimulation as acid enters the gullet.
 - Extra-esophageal:
 - Atypical chest pain (mimicking angina)
 - Chronic cough, asthma (often poorly controlled)
 - Laryngitis, dental erosions
 - Recurrent chest infection
- **Diagnosis:**
 - Based on history and empiric trial of proton pump inhibitors (PPI) – omeprazole.
 - **Endoscopy is the investigation of choice.** It is done when:

- Failure to respond to PPI.
- Alarm symptoms => 55 years, dysphagia, anemia, weight loss, positive fecal occult blood test.
- If diagnosis uncertain and endoscopy is normal, then:
 - Manometry = decreased LES pressure
 - **24-hour pH monitoring is the most accurate investigation.**


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Treatment:

- Lifestyle Modifications:
 - Avoid precipitants; lose weight; elevate the head of bed.
 - Avoid large and late-night meals,
- Treatment Algorithm:
 - In symptomatic patients start PPI at full dose:
 - If patient has good response – continue PPI at maintenance dose.
 - If patient has poor response – perform 24-hour pH monitoring:
 - If positive (i.e. acidic) – perform surgical fundoplication
 - If negative – reconsider diagnosis, tricyclic anti-depressants, SSRIs,
- Pharmacologic:
 - (i). Proton Pump Inhibitors:
 - PPIs are represented by omeprazole, lansoprazole, and esomeprazole.
 - **PPIs are the treatment of choice.**
 - PPIs reduced gastric acid production by inhibiting H⁺/K⁺ ATPase.
 - PPIs relieve both the symptoms and esophagitis.
 - Side effects = headache, diarrhea, increased risk of Clostridium difficile infection
 - (ii). H₂-Receptor Antagonist:
 - These are represented by cimetidine, ranitidine, and famotidine.
 - These block the action of histamine on parietal cells & decrease acid secretion.
 - These drugs relive only the symptoms, without healing esophagitis.
 - Side effects = headache, diarrhea, hypotension, gynecomastia (cimetidine)
- Surgery:
 - Indications:
 - Failure of medical therapy
 - Unwilling to take long-term PPIs
 - Severe regurgitation
 - Barrett's esophagus

▪ **Complications of GERD:**

- Esophagitis
- Barrett's esophagus
- Iron deficiency anemia – (blood loss from long-standing esophagitis)
- Benign esophageal stricture
- Gastric volvulus (if hiatal hernia present)

II. Hiatal Hernia:

- It is defined as herniation of stomach upward into the chest through esophageal hiatus of diaphragm.

▪ **Types:**

- Sliding Hernia (Axial):
 - It is the most common type; 95% of cases.
 - It refers to herniation of proximal stomach through a widened diaphragmatic hiatus.
 - The gastroesophageal junction is displaced above the diaphragm.
- Rolling Hernia (Non-axial):
 - It is also known as paraesophageal hernia.
 - It refers to herniation of portion of stomach (greater curvature) alongside the distal esophagus.
 - The gastroesophageal junction remains at the level of diaphragm.

▪ **Clinical Features:**

- Often asymptomatic
- Commonly an incidental finding on CXR
- Heartburn and regurgitation can occur
- Para-esophageal hernia can cause gastric volvulus.

III. Infectious Esophagitis:

- It usually occurs in immunocompromised individuals.
- It presents with odynophagia i.e. painful swallowing.

(i). Herpes Simplex Virus:

- It typically produces “punched-out” ulcers; ulcers are small, but deep.
- It forms multi-nucleated giant cells with **intra-nuclear inclusions** in epithelial cells at the margin of ulcer.
- Treatment = IV acyclovir

(ii). Cytomegalovirus:

- It typically produces "linear" ulcers; ulcers are large, but superficial.
- It forms both **intra-nuclear and intra-cytoplasmic inclusions**.
- Treatment = IV gancyclovir

(iii). Candida Albicans:

- It forms patchy gray-white pseudomembrane.
- It produces yeast and densely matted fungal hyphae.
- Treatment = oral fluconazole, OR, Nystatin oral suspension

IV. Barrett Esophagus:

Introduction:

- It is a pre-malignant condition.
- It is characterized by replacement of the normal squamous epithelium by the more resistant columnar epithelium containing areas of intestinal metaplasia.
- It occurs as a complication of long-standing GERD (10% cases).
- Risk Factors:
 - Men (especially white)
 - Age > 50 years
 - Weakly associated with smoking
 - No association with alcohol

Types:

- Short Segment Barrett = < 3 cm of columnar epithelium extending cephalad from GE-junction.
- Long Segment Barrett = ≥ 3 cm of columnar epithelium extending cephalad from GE-junction (aka Classic Barrett)

Diagnosis:

- Endoscopic biopsy – investigation of choice.
- Definitive diagnosis: when the columnar mucosa contains intestinal goblet cells, "intestinal metaplasia".

Management:

- Barrett Metaplasia without dysplasia = PPIs and endoscopy every 2 – 3 years
- Low-grade dysplasia = PPIs and endoscopy every 6 – 12 months
- High-grade dysplasia = Esophagectomy (surgical resection)



Clinical Pearl: **Barrett Esophagus:**

- Current definition of Barrett's esophagus requires two factors:
 1. Endoscopically visible columnar metaplasia irrespective of length
 2. Histological finding of intestinal metaplasia (with goblet cells)

▪ **Complications:**

- Ulceration with stricture formation (most common)
- Adenocarcinoma:
 - Short-segment = with unknown increased rate
 - Long-segment = 30 – 40 fold increased rate

Esophageal Tumors:

(A). Benign Tumors:

- The most common is a gastrointestinal stromal tumor (GIST).
- Other tumors are of following types:
 - Leiomyomas
 - Fibromas
 - Lipomas

(B). Esophageal Carcinoma:

I. Introduction:

▪ **Squamous Cell Carcinoma:**

- It is the most common type of esophageal carcinoma.
- It is male-dominant and occurs in adults over 50 years of age.
- It is most common in upper and middle thirds of esophagus.
- Risk factors:
 - Betel chewing
 - Tobacco use
 - Alcohol
 - Achalasia
 - Plummer-Vinson syndrome
 - Celiac disease

▪ **Adenocarcinoma:**

- It is malignant epithelial tumor with glandular differentiation.
- It is more prevalent in the West.
- It is most common in lower thirds of esophagus.

- Risk factors:
 - Barrett esophagus (most common) – lifetime risk is 10%
 - Tobacco; Obesity
 - Helicobacter pylori – not clear yet

II. Clinical Features:

▪ Presentation:

- Asymptomatic (early)
- Age > 55 years.
- Progressive dysphagia:
 - Dysphagia begins for solids only (unlike achalasia)
 - Dysphagia then occurs with liquids too as the disease progresses.
- Weight loss and anorexia
- Bleeding
- Hoarseness – involvement of recurrent laryngeal nerve.
- Chest pain – suggests mediastinal invasion.

▪ Metastasis:

- Local extension occurs early due to absence of serosa.
- Hematogenous spread:
 - Liver; lungs
 - Brain; bones

III. Management:

▪ Diagnosis:

- Endoscopy and biopsy – investigation of choice
- CT scan (thoracic & abdominal) – to identify metastatic spread and local invasion.
- Endoscopic ultrasound (EUS) is the most sensitive method for determining:
 - Depth of penetration of tumor into the esophageal wall.
 - Detecting involved regional lymph nodes.

▪ Treatment:

- Surgical resection is treatment of choice.
- Surgery is combined with chemo-radiotherapy.
- However, 70% of patients have extensive disease at presentation, and therefore treatment is mainly palliative.
 - Stent placement to keep esophagus patent and relieve dysphagia.
 - Nutritional support and analgesia

Stomach & Duodenal Diseases

Gastritis:

- It refers to inflammation of gastric mucosa.
- It may be acute or chronic.

I. Acute Gastritis:

- It is acute inflammation of gastric mucosa.
- It is caused by:
 - NSAIDS
 - Alcohol
 - Smoking
 - Brain injury (Cushing ulcer)
 - Burn injury (Curling ulcer)
 - Uremia
 - Stress
- Presentation:
 - Asymptomatic (early)
 - Epigastric pain
 - Nausea and vomiting
 - Massive hematemesis
 - Melena and fatal blood loss
- Treatment:
 - Treat the underlying cause.
 - Symptomatic treatment with antacids, PPIs, and anti-emetics

I. Chronic Gastritis:

- It is chronic inflammation of gastric mucosa, leading to mucosal atrophy and intestinal metaplasia, in the absence of erosions.
- It is usually of two types:

(i). Type-A Chronic Gastritis:

- It is autoimmune gastritis that involves the body and fundus.
- It is less common accounting for just 10% of cases of chronic gastritis.
- It is due to formation of autoantibodies against parietal cells and therefore affects:
 - HCl production = achlorhydria with hyper-gastrinemia
 - Intrinsic factor = pernicious anemia (vitamin B-12 deficiency)

- Associations:
 - Hashimoto thyroiditis
 - Addison disease
 - Type-1 diabetes
 - Gastric adenocarcinoma – four fold increased risk

(ii). Type-B Chronic Gastritis:

- It is the most common type of chronic gastritis.
- It involves the antrum and pylorus.
- The predominant inflammatory cells are lymphocytes and plasma cells.
- Treatment:
 - Most patients are asymptomatic and don't require therapy.
 - Patients with dyspepsia may benefit from H. pylori eradication (see below)

Menetrier Disease:

- Also known as "hypertrophic gastropathy".
- It results from hyperplasia of surface mucous cells with glandular atrophy.
- Gender = male-dominant; Etiology = unknown.
- Site = body-fundus, or entire stomach
- Features:
 - Gastric secretions contain excessive mucus.
 - Gastric secretions lack HCl (due to glandular atrophy).
 - Hypoalbuminemia (a form of protein-losing enteropathy)
 - Peripheral edema
 - Malignant transformation
 - Treatment = partial gastrectomy

Peptic Ulcer Disease (PUD):

I. Introduction:

- PUD is characterized by formation of ulcers that occur in any portion of GIT.
- PUD is caused by the action of gastric secretions and impaired mucosal defenses.
- **Locations:**
 - Duodenum = first portion of duodenum (most common)
 - Stomach = lesser curvature within the antrum (most common)
 - Gastroesophageal junction
 - Within or adjacent to an ileal Meckel diverticulum.
- **Causes:**
 - Chronic use of NSAIDs and aspirin
 - Steroids

- Smoking
- H. pylori infection:

- **Helicobacter Pylori:**

- It is a Gram-negative curved rod.
- It is strongly associated with PUD; these infections are probably acquired in childhood.
- It is transmitted by fecal-oral or oral-oral route.
- It is present in 90% of duodenal ulcers, 70% in gastric ulcers.
- It produces urease that buffers that gastric acid by forming ammonia and carbon dioxide.
- It produces pro-inflammatory cytokines (IL-1 and TNF)
- Other factors important in pathogenesis are:
 - Vacuolating cytotoxin (vacA)
 - Cytotoxin associated gene (cagA)
 - Adhesins (BabA)
 - Outer inflammatory protein A (oip A)

II. Presentation:

- **Clinical features:**

- Burning epigastric pain.
- Pain is worst at night and occurs 1-3 hours after meals.
- Pain due to **gastric ulcer is aggravated with food.**
- Pain due to **duodenal ulcer is relieved with food.**
- Pain may be referred to back, left upper quadrant, or chest.
- Occasional vomiting (in 40% cases) and weight loss.

- **Complications:**

- Bleeding (most common)
 - Gastric ulcer = from erosion of left gastric artery
 - Duodenal ulcer = from erosion of gastro-duodenal artery
- Perforation
- Gastric outlet obstruction
- Pancreatitis
- Malignant transformation:
 - Gastric ulcers associated with 1 – 4% increased risk.
 - Duodenal ulcers are NEVER malignant.

III. Diagnosis:

- Endoscopy is the investigation of choice.
- Screening for H. pylori

Test	Advantages	Disadvantages
Non – Invasive Tests		
Serology	Cheap; if negative it easily excludes infection	If positive, it cannot differentiate between current and previous infection
C ¹³ Urea Breath Test	Positive only in active infection	Requires expensive equipment
Fecal Antigen Test	Positive only in active infection	Acceptability (requires stool sample)
Invasive Tests		
Endoscopic Biopsy	The most accurate test of all	Invasive procedure
Rapid Urease Test	Cheap, quick, specific	Low sensitivity
Microbiological culture	“Gold standard”, define antibiotic sensitivity	Slow and laborious process Low sensitivity

IV.

R_x

Treatment:

If H. pylori is positive = eradication therapy:

- It consists of a PPI taken simultaneously with 2 antibiotics (from amoxicillin, clarithromycin, and metronidazole, tetracycline, and bismuth) for 10 – 14 days.
- Examples of regimes are:
 - (i). Triple Therapy:
 - Omeprazole 20 mg + Clarithromycin 500 mg + amoxicillin 1 g – all twice daily
 - Omeprazole 20 mg + Clarithromycin 500 mg + metronidazole 400 mg – all twice daily.
 - (ii). Quadruple Therapy:
 - It is given in eradication failures for 14 days.
 - Bismuth chelate (120 mg 4 x daily) + metronidazole (400 mg 3 x daily), tetracycline (500 mg 4 x daily) and PPI (20 – 40 mg 2 x daily) for 14 days.
- Tests to Check Eradication:
 - Perform urea breath test – OR – stool antigen test.
 - These tests are positive ONLY in active infection, which means failure of eradication.



Clinical Pearl:

PUD:

- Perform endoscopy in patients with gastric ulcer & persistent symptoms.
- This is important to rule out gastric malignancy.
- Patients requiring long-term NSAIDs:
 - First complete eradication therapy
 - Then start co-prescription of PPI along with NSAID
 - PPI is however not necessary in patients on low-dose aspirin (can use misoprostol)

▪ If H. pylori is negative = acid suppression therapy:

- PPIs (suppress gastric acid)
- Discontinue aspirin or NSAIDs
- Lifestyle changes – smoking cessation
- Surgery in refractory cases.

▪ Prophylaxis in Patients Requiring Aspirin NSAIDs:

- Use PPI, if:
 - History of PUD/Upper GI bleeding
 - Also taking clopidogrel
 - ≥ 2 of the following – age > 60 , steroids, dyspepsia, prior to start test & treatment of H. pylori

▪ Surgery in PUD:

○ Indications:

- Emergency:
 - Perforation
 - Hemorrhage
- Elective:
 - Complications (e.g. gastric outlet obstruction)
 - Recurrent ulcer following gastric surgery

○ Methods:

- Billroth – I Operation:
 - It is for gastric ulcer.
 - Resection of distal stomach and anastomosis directly to duodenum.
- Billroth – II Operation:
 - It is for duodenal ulcer.

- Resection of distal two-thirds of stomach, & a loop of jejunum is brought up and joined to it for drainage; duodenum is closed-off.

○ **Complications of Surgery:**

- Recurrent ulceration
- Bile-reflux gastritis
- Early dumping:
 - It occurs immediately after taking meals.
 - It is characterized by epigastric fullness, sweating, lightheadedness, tachycardia, colic, and diarrhea.
- Late dumping:
 - It occurs few hours after taking meals.
 - It is reactive hypoglycemia characterized by tremors, faintness, and prostration.

Zollinger–Ellison Syndrome (ZES):

I. Introduction:

- It is a condition characterized by gastrin-producing tumors in the duodenum and/or pancreas that lead to over-secretion of gastrin, which increases gastric acid production.
- It is characterized by a triad of:
 - Severe peptic ulceration
 - Gastric acid hypersecretion
 - Gastrinoma (non-beta cell islet tumor of the pancreas ± duodenum)

II. Clinical Features:

- Always suspect this diagnosis when a patient presents with peptic ulcers that are:
 - Large (> 1-2 cm)
 - Recurrent (after H. pylori eradication)
 - Unusual sites such as distal duodenum, jejunum, esophagus
 - Multiple
- Association:
 - Diarrhea in one-third cases.
 - MEN type-I in 20 – 60% of patients.
 - Hypercalcemia in patient with ZES should always raise the suspicion for MEN type-I (hyperparathyroidism causes hypercalcemia)

III.

Rx

Management:▪ **Diagnosis:**

○ Confirmatory Tests:

- High serum gastrin levels (10 – 1000 fold)
- High gastrin levels, despite high gastric acid output.
- Secretin hormone injection:
 - In normal individuals = no change or slight decrease in gastrin secretion
 - In ZES = paradoxical and dramatic increase in gastrin secretion.

○ Localization of tumor:

- Endoscopic ultrasound (EUS) = best test to localize tumor
- Radio-labelled somatostatin receptor scintigraphy

▪ **Treatment:**

- High dose PPIs (e.g. omeprazole 60 – 80 mg daily)
- Localized diseases (only 30%) = surgical resection
- Metastatic disease:
 - Life-long PPI therapy
 - Octreotide

Tumors of Stomach:**I. Gastric Carcinoma:**

- It is the most common malignant tumor of stomach.
- Most common site:
 - Developing world = antrum (lesser curvature)
 - Developed world = proximal gastric tumors (fundus)
- **Risk factors:**
 - Environmental factors:
 - **H. pylori – most important**
 - Nitrites
 - Smoked fish and meats
 - Smoking
 - Host factors:
 - Chronic gastritis; Menetrier disease
 - Gastric adenomas; Barrett esophagus
 - Genetic factors:
 - Blood group A

- Family history
- Male predominance
- Familial gastric carcinoma syndrome
- Hereditary non-polyposis colon cancer (HNPCC)

▪ **Morphology:**

(i). Depth of Invasion:

- Early gastric carcinoma:
 - It is gastric carcinoma confined to mucosa and submucosa regardless of the presence or absence of perigastric lymph node metastases.
- Advanced gastric carcinoma:
 - It is gastric carcinoma that has extended below the submucosa into the muscular wall and has perhaps spread more widely.

(c). Histologic Subtype (**Lauren Classification**):

- Intestinal type (common):
 - Arises from areas of intestinal metaplasia.
 - Expanding growth pattern.
- Diffuse type:
 - Arises from normal gastric mucosa.
 - Infiltrating growth pattern.
 - Linitis plastica, thickened leather-bottle like stomach.
 - Signet-ring cell carcinoma is defined when > 50% of tumor is formed by signet-ring cells.

▪ **Metastasis:**

- To left supraclavicular node (Virchow node) – Troisier's sign
- To periumbilical region to form a subcutaneous nodule (Sister Mary Joseph nodule)
- To ovaries (**Krukenberg tumor**)

▪ **Presentation:**

- Asymptomatic (early)
- Weight loss and anorexia
- Epigastric pain
- Occult bleeding
- Iron deficiency anemia
- Paraneoplastic skin lesions:
 - Acanthosis nigricans
 - **Leser-Trelat syndrome** – multiple outcroppings of seborrheic keratosis

▪ **Diagnosis:**

- Upper GI endoscopy – investigation of choice
- Staging:
 - CT scan
 - Laparoscopy:
 - It is the only modality that will reliably detect peritoneal spread.
 - It therefore determines whether the tumor is resectable or not.

R_x

Treatment:

- Surgery – offer the only hope of cure.
- Surgery is curative in 90% of patients with early gastric cancer.
- Peri-operative chemotherapy with epirubicin, cisplatin and fluorouracil (ECF) improves survival rates.

▪ **Prognosis:**

- Prognosis depends on two factors:
 - Depth of invasion
 - Extent of nodal and distant (visceral) metastasis
- 5- year survival rate:
 - Early gastric cancer = 90 – 95%
 - Advanced gastric cancer = 15%

II. Gastric Lymphoma:

- Gastric lymphomas represent 5% of all gastric malignancies.
- The stomach is however, the most common site for extra-nodal non-Hodgkin's lymphoma.
- Risk Factors:
 - Chronic gastritis
 - H. pylori infection
- Gastric lymphomas are of two types:
 - Low-grade lymphoma (MALToma) – associated with H. pylori
 - High-grade lymphoma

R_x

Treatment:

- Low grade lymphoma:
 - H. pylori eradication therapy.
 - 25% cases contain t(11: 18) translocations and will not respond to eradication.
 - These cases are treated with radiotherapy or chemotherapy.
- High-grade lymphoma:
 - Surgery, plus
 - Chemotherapy + radiotherapy



Clinical Pearl:

MALT-lymphoma:

- It is the ONLY malignancy that can be cured with antibiotics.
- It is treated with triple-therapy:
 1. Amoxicillin
 2. Clarithromycin
 3. Omeprazole

MALT = mucosa associated lymphoid tissue

III. Other Tumors:

- Gastrointestinal Stromal Tumors (GIST) = Originate from interstitial cells of Cajal.
- Metastatic Cancers = from systemic lymphomas (most common)
- Carcinoid (Neuroendocrine cell) Tumor = Originate from enterochromaffin-like cells (ECL cells)

Gastrointestinal Bleeding:

I. Introduction:

- GI bleeding is defined as intra-luminal blood loss anywhere from the oropharynx to the anus.
- Classification:
 - Upper GI bleeding = occurs above ligament of Treitz (marks duodeno-jejunal junction)
 - Lower GI bleeding = occurs below ligament of Treitz.

II. Upper Gastrointestinal Bleeding (UGIB):

- UGIB is the most common gastrointestinal emergency.
- **Symptoms:**
 - Hematemesis = blood in vomitus:
 - Very severe = red color with clots
 - Less severe = black vomitus (coffee-ground emesis)
 - Melena:
 - It refers to black, tarry stools from digested blood.
 - It is mostly due to UGIB.
 - However, it can occur with bleeding from any lesion proximal to right colon.
- **Causes:**
 - **Peptic ulcer disease – most common cause**
 - Gastric erosions (NSAIDs, alcohol)
 - Esophagitis
 - Esophageal varices
 - Mallory – Weiss tear:
 - It refers to longitudinal tear at gastroesophageal junction.
 - It is due to retching (severe vomiting) against closed glottis.
 - Vascular malformation:
 - Aorto-enteric fistula – abdominal aortic aneurysm or aortic graft erodes into the 3rd portion of duodenum.
 - **“Dieulafoy’s lesion”:**
 - It refers arteriovenous malformation,
 - It is mostly on lesser curvature of stomach; presenting with sudden, massive UGIB.



Treatment:

- Gain intravenous access with large-bore cannula.
- Basic investigations:
 - CBC:
 - Chronic, sub-acute bleeding = anemia
 - Sudden, massive bleeding = normal hemoglobin until hemodilution occurs
 - Urea & electrolytes:
 - Evidence of renal failure
 - Elevated blood urea with normal creatinine implies severe bleeding.
 - LFTs and PT
 - Cross-matching of at least 2 units of blood.
- Assess severity:
 - Hourly measurement of blood pressure, pulse, urine output and central venous pressure (severe bleeding)
 - Tachycardia suggests 10% volume loss, orthostatic hypotension 20% loss, shock > 30% loss.
- Resuscitation:
 - Volume replacement = normal saline or Ringer lactate.
 - **Hemoglobin is a poor indicator of the need to transfuse.**
 - Hematocrit is better indicator of the need to transfuse.
 - Use O – negative blood in case of emergency.
 - Rough guide for the need to transfuse:
 - Hemoglobin level < 10 g/dL + active bleeding.
 - Hematocrit < 30 = in older people, or those with coronary artery disease
 - Hematocrit 20 – 25 = in young patients
- Important Measures:
 - Oxygen by facemask to all patients in shock.
 - Fresh frozen plasma = if PT or INR is elevated and active bleeding.
 - Platelets = if the count is < 50, 000 and there is bleeding.
 - PPIs for bleeding peptic ulcer
 - Octreotide or terlipressin for variceal bleeding.
- Endoscopy:
 - It should be carried out after adequate resuscitation.
 - It is ideally performed **within 24 hours**, and will yield a diagnosis in 80% cases,

- After adequate resuscitation, **urgent endoscopy** should be performed in patients with shock, suspected varices, or continued bleeding.
- Endoscopy has the advantage of therapeutic significance, example:
 - Varices can be treated with banding.
 - Bleeding ulcers can be treated by injection of epinephrine and thermal coagulation.
- Surgery:
 - It is indicated in following cases:
 - Endoscopy fails to control active bleeding
 - Re-bleeding occurs on 1 occasion in an elderly, frail patient.
 - Re-bleeding occurs on 2 occasions in a young, fitter patient.

III. Lower GI Bleeding:

▪ Symptoms:

- The pass of dark blood and clots without shock is always due to lower GI-bleeding.
- Hematochezia:
 - It refers to bloody stools; seen in LGIB.
 - It may be seen in rapid UGIB.

▪ Causes:

- Severe Acute LGIB:
 - Diverticular disease – most common
 - Angiodysplasia
 - Meckel's diverticulum
 - Bowel ischemia – due to occlusion of inferior mesenteric artery
- Chronic, Sub-acute LGIB:
 - Anal disease (e.g. fissure and hemorrhoids)
 - Carcinoma
- Occult GI Bleeding:
 - It means that blood or its breakdown products are present in stool, but cannot be seen by the naked eye.
 - Causes:
 - Cecal carcinoma – most common
 - Can be any cause of GI bleeding

▪ Diagnosis:

- Always rule out UGIB first before attempting to localize presumed LGIB, then colonoscopy (which identify cause in > 70% cases).
- Investigations:

- Capsule endoscopy:
 - It is used for diagnosis of small bowel bleeding.
 - It is used only when upper and lower GI – endoscopy do not show the etiology.
- Tagged RBC scan:
 - It is used when endoscopy fails to reveal diagnosis in massive, acute hemorrhage.
 - It can localize bleeding rates ≥ 0.1 mL/min.
- Arteriography:
 - It is used only in massive, non-responsive bleeding.
 - It identifies specific vessel or bleeding site prior to surgery or embolization.
- **Treatment:**
 - Initial management, resuscitation, and monitoring in the similar way as UGIB.
 - Treatment of Specific Causes:
 - Diverticular disease:
 - Bleeding stops spontaneously.
 - If it doesn't stop, the diseased segment of colon is surgically resected after confirmation by arteriography or colonoscopy.
 - Angiodysplasia:
 - Bleeding stops spontaneously.
 - If it doesn't stop, then treatment of choice is endoscopic thermal ablation.
 - If bleeding still continues, then surgical resection of affected bowel.
 - Bowel Ischemia:
 - Diagnosed by colonoscopy.
 - Resection is required only in the presence of peritonitis.

Diseases of Small Intestine

Malabsorption Syndromes:

- Malabsorption is characterized by defective absorption of fats, fat-soluble vitamins, proteins, carbohydrates, electrolytes and minerals, and water.
- The most common clinical presentation is chronic diarrhea,
- The hallmark of malabsorption is steatorrhea.
- Malabsorption syndromes can all present with deficiency of fat-soluble vitamins (A, D, E, K) and water-soluble vitamins and therefore following features:

<u>Deficiency</u>	<u>Manifestation</u>
Vitamin A	Night blindness, follicular hyperkeratosis
Vitamin D	Hypocalcemia, osteoporosis
Vitamin K	Bleeding, easy bruising
Vitamin B12	Anemia, hypersegmented neutrophils, neuropathy

I. Celiac Disease:

- Also known as "gluten-sensitive enteropathy".
- It is an autoimmune disease, characterized by hypersensitivity to gluten (and gliadin), resulting in loss of small bowel villi and malabsorption.
- Gluten is alcohol-soluble, water-insoluble protein component of wheat, oat, barley, and rye.
- **Pathogenesis:**
 - It is characterized by T-cell and IgA-mediated response against gluten in genetically susceptible individuals.
 - It is associated with HLA-DQ2 and HLA-DQ8.
 - Highest incidence in infancy.
- **Clinical Features:**
 - Females are affected twice as often as males.
 - Diarrhea, weight loss, flatulence.
 - Malnutrition, and osteoporosis
 - Anemia:
 - Microcytic anemia – from iron deficiency
 - Macrocytic anemia – from folate deficiency
 - **Dermatitis Herpetiformis:**
 - It is seen in 10% of cases
 - It is characterized by intensely pruritic, papulovesicular lesions on extensor surfaces of elbows, knees, and buttocks.

- Immunofluorescence shows IgA deposition at the dermo-epidermal junction.
- Treatment:
 - Best Initial Treatment - gluten-free diet
 - Next Best Step - Dapsone (100 – 150 mg daily)
- Presentation in children:
 - Infancy:
 - It presents after weaning on to cereals.
 - It presents with diarrhea, malabsorption, and failure to thrive.
 - Children:
 - Growth and pubertal delay.
 - Short stature.
- **Association:**
 - Celiac disease is associated with other human leukocyte antigen (HLA) – linked autoimmune disorders:
 - Insulin dependent diabetes (type-I)
 - Hashimoto's thyroiditis
 - Primary biliary cirrhosis
 - IgA deficiency
 - Myasthenia gravis
 - **Non-Hodgkin lymphoma:**
 - It is enteropathy-associated T-cell lymphoma.
 - It is the most common malignant complication.
 - It is due to large amount of **Interleukin-15** production by epithelial cells.
- **Diagnosis:**
 - Endoscopic Biopsy:
 - It is the **Gold-standard test**.
 - It gives characteristic morphologic features:
 - Most common site = duodenum and proximal jejunum.
 - Chronic intra-epithelial inflammatory infiltrate (lymphocytic).
 - **Villous atrophy and blunting.**
 - Crypt hyperplasia.
 - Anti-tissue Transglutaminase (tTG) IgA Antibodies:
 - It is excellent screening test.
 - It is more accurate in patients with IgA deficiency.
 - Anti-endomysial IgA Antibodies:
 - Sensitivity (85-95%) and specificity is 100%.
 - Excellent screening test.

- Anti-gliadin IgA Antibodies:
 - Sensitivity 80%, specificity 85%
 - Moderately good screening test.
- **Treatment:**
 - Mainstay of Treatment:
 - **Life-long GLUTEN-free diet.**
 - This requires omission of wheat, rye, barely, and oats (oats can be started later)
 - Correction of deficiencies – Iron, Folate, Calcium, Vitamin D
 - Refractory cases = corticosteroids; immunosuppressants



Clinical Pearl:

Difference between Celiac Disease & Chronic Pancreatitis:

- Both of them cause malabsorption.
- Chronic pancreatitis is not associated with iron or folate deficiency.
- Celiac disease is associated with iron and folate deficiency.
- D-xylose test: normal reabsorption is seen in chronic pancreatitis.
- D-xylose test: decreased reabsorption is seen in celiac disease.

II. Whipple Disease:

- It is systemic infectious disease that may involve any organ, but principally affects intestine, CNS, and joints.
- It is caused by bacterium **Tropheryma whippelii**, which are gram-positive actinomycetes.
- Age = 40 – 50 years
- **Gender = MALE dominant (M:F 10:1)**
- **Clinical Features:**
 - Gastrointestinal (>70%):
 - Weight loss,
 - Diarrhea, bloating, steatorrhea,
 - Protein-losing enteropathy
 - Hepatosplenomegaly
 - Musculoskeletal (65%):
 - Seronegative large joint arthropathy; sacroiliitis
 - It is often the initial presentation
 - Neurologic (10 – 40%):

- Seizures, dementia, cranial nerve palsies.
- **Oculomasticatory Myorhythmia:**
 - Eye oscillations, PLUS:
 - Rapid contraction of muscles of mastication
- Other Features:
 - Cardiac = pericarditis, myocarditis, endocarditis
 - Pulmonary = chronic cough, infiltrates
 - Fever, anemia, skin pigmentation,
 - Lymphadenopathy
- **Diagnosis:**
 - Endoscopic Biopsy:
 - It is the **Gold-standard test**.
 - It gives characteristic morphologic features:
 - Villous atrophy and blunting.
 - **Hallmark feature = distended macrophages in the lamina propria of small intestinal mucosa.**
 - Foamy macrophages containing PAS-positive granules in lamina propria.
- **Treatment:**
 - Intravenous Ceftriaxone 2g daily for 2 weeks.
 - Followed by oral co-trimoxazole for at least 1 year.

III. Lactose Intolerance:

- It is due to deficiency of lactase, which normally converts lactose to glucose & galactose.
- Lactase is a brush border enzyme of the villous absorptive epithelial cells.
- **Etiology:**
 - Primary LI - is due to genetic deficiency of the enzyme
 - Secondary LI - is due to damage to jejunal mucosa – celiac disease, viral gastroenteritis
- **Features:**
 - Chronic diarrhea with increased osmotic gap.
 - Diarrhea is explosive, watery with bloating and abdominal distention.
 - Negative fecal fat (i.e. no steatorrhea)
 - Diarrhea decreases with fasting.
 - No vitamin deficiency
 - No weight loss.

▪ **Diagnosis:**

- Hydrogen breathe test.
- Improvement of symptoms after lactose-free diet.

▪ **Treatment:**

- Lactose-free diet.
- Lactase enzyme tablets

IV. Bacterial Overgrowth Syndrome:

- Also known as "Blind Loop Syndrome".
- In normal small bowel the count of coliform organisms never exceeds $10^3/\text{mL}$.
- In bacterial overgrowth syndrome the count of coliform organism may be $10^8 - 10^{10}/\text{mL}$.

▪ **Causes:**

- Hypochloridia:
 - Pernicious anemia
 - Partial gastrectomy
- Impaired Intestinal Motility:
 - Scleroderma
 - Diabetic autonomic neuropathy
- Structural Abnormalities:
 - Strictures (Crohn's disease, TB)
 - Enterocutaneous fistulas (Crohn's disease, TB)
 - Extensive small bowel resection
 - Jejunal diverticulosis

▪ **Clinical Features:**

- Watery diarrhea, Steatorrhea.
- Anemia due to vitamin B12 deficiency
- Serum folate levels are normal or elevated because the bacteria produce folic acid.
- **Diagnosis:**
 - Barium follow-through
 - Endoscopic small bowel biopsy
 - Glucose hydrogen breath test = bacteria increases breath hydrogen
 - ^{14}C -glycocholic acid breath test = bacteria increases breath ^{14}C .

▪ **Treatment:**

- Treat the underlying cause.
- Tetracycline 250 mg 6-hourly for 7 days is then the treatment of choice.
- Alternative:
 - Metronidazole 400 mg 8-hourly
 - Ciprofloxacin 250 mg 12-hourly

V. Abetalipoproteinemia:

- It is an autosomal recessive disorder.
- It is caused by deficiency of apolipoprotein B, which results in failure of chylomicron formation.
- **Diagnosis:**
 - Fat malabsorption
 - Fat-soluble vitamin deficiency
 - Low serum cholesterol & triglycerides
 - Jejunal Biopsy:
 - **Enterocytes distended with re-synthesized triglycerides**
 - Normal villous morphology.
 - Associations:
 - Acanthocytosis, Retinitis pigmentosa
 - Progressive neurologic disorder – cerebellar & dorsal column signs
- **Treatment:**
 - **Low-fat diet, supplemented with medium-chain triglycerides**
 - Supplementation with fat-soluble vitamins – A, D, E, K.

Meckel Diverticulum:

I. Introduction:

- It is a congenital anomaly due to failure of involution of the vitelline duct, which connects the developing gut to the yolk sac.
- It is a true diverticulum as it contains all three layers of the normal bowel wall.
- It lies on antimesenteric side of the bowel.
- **Rule of “2”:**
 - 2 inches long
 - 2 feet (85 cm) from ileocecal valve
 - 2% of population
 - 2% symptomatic
 - 2 types of ectopic tissue:
 - Pancreatic tissue
 - Gastric tissue

II. Diagnosis & Management:

- **Clinical Features:**
 - Painless severe hemorrhage
 - Intussusception
 - Diverticulitis
 - Chronic peptic ulceration
 - Intestinal obstruction
- **Management:**
 - **Technetium-99m pertechnetate scan is the investigation of choice.**
 - **Surgical excision is the treatment of choice.**

IBD & IBS

Inflammatory Bowel Disease (IBD):

- It is a set of chronic inflammatory conditions resulting from inappropriate and persistent activation of the mucosal immune system.
- It is represented by:
 - Crohn's Disease (CD)
 - Ulcerative Colitis (UC)

<u>Ulcerative Colitis</u>	<u>Crohn's Disease</u>
<u>Definition:</u> It is chronic relapsing ulcero-inflammatory disease, and the most common IBD.	<u>Definition:</u> It is chronic granulomatous, ulcero-constrictive disease.
<u>Epidemiology:</u> <ul style="list-style-type: none"> ▪ No sex predilection ▪ Smoking has protective effect. ▪ Peak occurs at 20 – 30 years ▪ Usually affects young adults 	<u>Epidemiology:</u> <ul style="list-style-type: none"> ▪ Female > male ▪ Strong association with smoking. ▪ Bimodal age distribution: first peak at 10 – 30 and second peak at 50 – 70. ▪ Usually affects young adults
<u>Genetics:</u> <ul style="list-style-type: none"> ▪ It is a complex multigenic trait, and is not inherited in Mendelian fashion. ▪ HLA-DR2 ▪ Excessive activation of TH2-subset of helper T-cells. ▪ Perinuclear anti-neutrophilic cytoplasmic antibody i.e. (p-ANCA) = 75% ▪ Anti-Saccharomyces cerevisiae antibody i.e. (ASCA) = absent 	<u>Genetics:</u> <ul style="list-style-type: none"> ▪ It is a complex multigenic trait, and is not inherited in Mendelian fashion. ▪ HLA-DR1 + NOD-2 mutations ▪ Excessive activation of TH1-subset of helper T-cells. ▪ Perinuclear anti-neutrophilic cytoplasmic antibody i.e. (p-ANCA) = 11% ▪ Anti-Saccharomyces cerevisiae antibody i.e. (ASCA) = present
<u>Location:</u> <ul style="list-style-type: none"> ▪ Rectum (most common) ▪ Extend proximally in a retrograde fashion to involve the entire colon. ▪ Doesn't involve other areas of GIT 	<u>Location:</u> <ul style="list-style-type: none"> ▪ Small intestine (terminal ileum) = 40% ▪ Ileum and colon = 30% ▪ Colon alone = 30% ▪ Involves other areas of GIT (mouth to anus)

<u>Ulcerative Colitis</u>	<u>Crohn's Disease</u>
Gross Features: <ul style="list-style-type: none"> ▪ Pseudopolyps ▪ Areas of friable, bloody residual mucosa ▪ Hemorrhage ▪ Extensive broad-based ulceration ▪ "Backwash ileitis" i.e. it may spread backward to involve the ileum due to incompetence of ileocecal valve. ▪ No skip lesions i.e. mucosal damage is continuous. 	Gross Features: <ul style="list-style-type: none"> ▪ Aphthous ulcers (early sign) ▪ Thick bowel wall and narrow lumen ▪ Fissures ▪ Serpentine linear ulceration ▪ Creeping fat i.e. the bowel surface is wrapped by the mesenteric fat. ▪ Skip lesions are formed due to discontinuous spread.
Microscopy: <ul style="list-style-type: none"> ▪ Inflammation limited to mucosa and submucosa. ▪ No granulomas seen. ▪ Crypt abscesses containing neutrophils ▪ Dysplasia or cancer likely to be present. 	Microscopy: <ul style="list-style-type: none"> ▪ Transmural inflammation (affects all the layers) ▪ Noncaseating granulomas ▪ Lymphoid aggregates. ▪ Dysplasia or cancer less likely
Radiography: <ul style="list-style-type: none"> ▪ "Lead pipe" appearance from loss of haustration 	Radiography: <ul style="list-style-type: none"> ▪ "String" sign in terminal ileum from luminal narrowing.

I. Clinical Features & Management of UC:

Clinical Features:

- Recurrent left-sided abdominal cramping with bloody diarrhea.
- Attacks are precipitated by periods of physical and emotional stress.
- Complications:
 - Toxic megacolon (hypotonic and distended bowel)
 - Adenocarcinoma of colon
- Extra-colonic Manifestations:
 - Primary sclerosing cholangitis
 - Ankylosing spondylitis
 - Migratory polyarthritis
 - Pyoderma gangrenosum
 - Erythema nodosum
 - Uveitis, episcleritis
 - Thromboembolic events

■ Investigations:

- Iron deficiency anemia
- Raised ESR and CRP
- p-ANCA = positive
- Stool cultures = to exclude infective causes of colitis
- Plain abdominal X-ray = "lead-pipe" appearance from loss of haustration
- Colonoscopy:
 - It defines the extent and activity of disease.
 - **It shouldn't be performed in acute severe attack (risk of perforation)**


 Rx

Treatment:

- Active Proctitis:
 - It involves only the rectum.
 - Oral aminosalicylates plus local rectal steroid preparation.
- Left-sided Proctocolitis:
 - It involves the rectum and left-sided colon.
 - Mild cases = oral aminosalicylates + local rectal steroid preparation.
 - Moderate-severe cases = oral aminosalicylates + oral steroids



Fulminant (Acute Severe) UC:

- Intravenous fluids
- Transfusion if Hb is < 10 g/dL.
- Intravenous steroids (e.g. IV methylprednisolone 60 mg daily)
- Antibiotics for proven infection
- Nutritional support
- Subcutaneous heparin for prophylaxis of venous thromboembolism.
- Consider infliximab (5mg/kg) in stable patients not responding to 3 – 5 days of steroids.
- Surgery:
 - Surgery is indicated when:
 - Failure of medical treatment:
 - In acute attack = after 3 days
 - Chronic cases without improvement
 - Toxic megacolon (> 6 cm colon on X-ray)
 - Hemorrhage
 - Perforation
 - Risk of cancer
 - Excessive steroid requirement

II. Clinical Features & Management of CD:

▪ Clinical Features:

- Recurrent right lower quadrant colicky pain with diarrhea.
- Attacks are precipitated by periods of physical and emotional stress.
- Bleeding occurs only with colon or anal involvement.
- Complications:
 - **Perianal disease** = anal fissure, anal fistula, anorectal abscess
 - **Fistula formation**; fibrosing strictures
 - **Calcium oxalate renal calculi**
 - Steatorrhea – malabsorption of bile acids.
 - Pernicious anemia, due to malabsorption of vitamin B12.
 - Protein-losing enteropathy, due to marked loss of albumin.

▪ Investigations:

- CBC = anemia
- Raised ESR and CRP
- ASCA = positive
- Barium-follow-through
- Contrast enhanced CT scan of abdomen
- Colonoscopy – if colonic involvement is suspected.
- Endoanal ultrasound and MRI – for perianal disease

R_x

Treatment:

- Acute exacerbation of CD:
 - Antibiotics = fluoroquinolones; **metronidazole is best for perianal disease.**
 - Mild, moderate, severe = corticosteroids
 - Severe disease unresponsive to steroids = give infliximab; cyclosporin A.
 - **Surgery:**
 - Failure of medical therapy with acute or chronic symptoms
 - Complications (obstruction, perforation, fistula)
 - Failure to grow (in children) despite treatment

III. Chronic Maintenance of Remission in UC & CD:

- Asacol (mesalamine) is used for UC.
- Pentasa (mesalazine) is used for CD.
- Rowasa (mesalazine) is used for UC largely limited to rectum.
- Azathioprine and 6-mercaptopurine are used to wean patients off steroid.

- Perianal Crohn's disease is treated with ciprofloxacin, and metronidazole.
- **Infliximab and adalimumab are best for enterocutaneous fistulae.**
- Surgery:
 - UC = **surgery is curative**; total colectomy
 - CD = surgery is not curative; only done for complications



Clinical Pearl:

IBD & Colon Cancer:

- IBD increases the risk for colon cancer (**especially UC**)
- Screening is therefore recommended with **colonoscopy** after 8 – 10 years of colonic involvement.
- Colonoscopy is done every 1 – 2 years.

IV. Important Pharmacologic Agents in IBD (Stepwise):

- **Step – I: Aminosalicylates:**
 - They are represented by mesalazine and sulfasalazine.
 - They are used in UC; no proven value in CD.
 - They are used both during acute flares & maintenance of remission.
 - They are safe during pregnancy.
 - Side effects (sulfasalazine):
 - Headache; diarrhea
 - Nephritis
 - Hemolysis, neutropenia
 - **Reversible infertility in males**
- **Step – II: Steroids:**
 - They are represented by prednisolone, hydrocortisone, and budesonide.
 - They have anti-inflammatory effect; used both in CD and UC.
 - They are used only during acute flares – **NO ROLE** in maintenance of remission.
 - Routes – IV, Oral, Topical.
- **Step – III: Immuno-modulators:**

Azathioprine:

 - It causes immune-modulation by inducing T-cell apoptosis.
 - It is safe during pregnancy.
 - Side effects:
 - Flu-like symptoms with myalgia
 - Leukopenia
 - Pancreatitis
 - Increased risk of lymphoma

Anti-Tumor Necrosis Factor (anti-TNF):

- They are represented by infliximab and adalimumab.
- They suppress inflammation and induce apoptosis of inflammatory cells.
- They are best for enterocutaneous fistulas of CD.
- Side-effects:
 - Arthralgias
 - Anaphylactic reaction after multiple infusions.
 - **Reactivation of tuberculosis.**
 - Increased risk of infections and malignancy
- **Step – IV: Clinical Trial Agents:**
 - CD - thalidomide, interleukin (IL) – 11
 - UC - nicotine patch, butyrate enema

Irritable Bowel Syndrome (IBS):

I. Introduction:

- It is the most common functional gastrointestinal disorder.
- It is characterized by recurrent abdominal pain in association with abnormal defecation in the ABSENCE of STRUCTURAL abnormality of the gut.
- **Clinical Features:**
 - Recurrent abdominal pain – most common symptom.
 - Abdominal pain is colicky or cramping in nature
 - Abdominal pain is felt in lower abdomen and relieved by defecation.
 - Abdominal bloating worsens throughout the day.
 - Passage of mucus is common, but rectal bleeding doesn't occur.
- **Trigger Factors:**
 - Factors that can trigger the onset of IBS:
 - Affective disorders (depression, anxiety)
 - Psychological stress and trauma
 - Gastrointestinal infection
 - Antibiotic therapy

II. Diagnostic Criteria:

Rome-III Diagnostic Criteria for IBS:

- Recurrent abdominal pain for ≥ 3 days per month over last 3 months.
- Plus ≥ 2 of following:
 1. Improvement with defecation
 2. Onset associated with a change in frequency of stool
 3. Onset associated with a change in form (appearance) of stool.

III.

Rx

Treatment:

- Pain = antispasmodics, tricyclic antidepressants, selective serotonin reuptake inhibitors.
- Bloating = Rifaximin, probiotics
- Diarrhea-Predominant IBS:
 - Step-1 = Avoid dietary fiber
 - Step-2 = Anti-diarrheal agents (loperamide, codeine, cholestyramine)
 - Step-3 = Tricyclic antidepressants (TCAs) – (amitriptyline, imipramine), Rifaximin
 - Step-4:
 - Duloxetine (30 – 60 mg at night)
 - Relaxation therapy
 - Biofeedback
 - Hypnotherapy
- Constipation-Predominant IBS:
 - Step-1 = High fiber diet
 - Step-2 = Bulk-forming agents (lactulose, ispaghula, psyllium)
 - Step-3 = 5-HT₄ agonist (Prucalopride)
 - Step-4 = (same as above)
- Pain & Bloating:
 - Step-1 = dietary changes (low FODMAP diet, exclude wheat, exclude dairy, gluten-free)
 - Step-2 = Spasmolytic drugs (hyoscine, peppermint oil), TCA, Rifaximin
 - Step-3 = (same as step-4, mentioned above)

Diseases of Colon & Rectum

Polyps & Polyposis Syndromes:

I. Non – Neoplastic Polyps:

- These are tumorous mass that protrudes into the lumen of the gut.
- These have no malignant potential, and arise as a result of abnormal mucosal maturation, inflammation, or architecture.
- These are of following types:
 - **Hyperplastic Polyps:**
 - These are the most common type of polyps (90%).
 - Most common site: rectosigmoid colon
 - **These have no malignant potential.**
 - But those occurring in the setting of “hyperplastic polyposis syndrome” have risk for carcinoma.
 - **Hamartomatous Polyps:**
 - These are malformations of the gland and mucosa.
 - (i). Juvenile Polyps:
 - Most common polyp in children.
 - No malignant potential; 1 – 3 cm in diameter.
 - Most common site = rectum.
 - (ii). Retention Polyps:
 - Hamartomatous polyps in adults.
 - No malignant potential; < 1cm in diameter.
 - Most common site = rectum.
 - (iii). Juvenile Polyposis Syndrome:
 - Autosomal dominant; mutations of SMAD4.
 - Characterized by 50 – 100 juvenile polyps in the GIT.
 - Malignant potential.
 - (iv). Peutz-Jeghers Syndrome:
 - Autosomal dominant; **mutations of STK11 on chromosome 19**
 - Hamartomatous polyps; **most common site = small bowel.**
 - Pigmentation of buccal mucosa and lips; increased risk for intussusception.
 - Associated with increased risk of colorectal, breast, and gynecologic cancers.

II. Adenomas:

- Adenomas are neoplastic polyps, also called “**adenomatous polyps**”.
- Adenomas are of following types:
 1. Tubular adenoma
 2. Villous adenoma
 3. Tubulovillous adenoma
 - Tubular Adenoma:
 - Most common adenoma; malignant potential.
 - Most common site = colon (90%)
 - Villous Adenoma:
 - Most common symptomatic adenoma.
 - Most common site = rectum and rectosigmoid colon.
 - Secrete protein and K-rich mucus (resulting in hypoproteinemia and hypokalemia)
 - **Greatest risk for developing colon cancer.**
 - Tubulovillous Adenoma:
 - Mixture of tubular glands and villous projections; malignant potential.
 - Mostly asymptomatic.

III. Familial Syndromes:

A. Familial Adenomatous Polyposis (FAP):

(i). Introduction:

- Inheritance = autosomal dominant
- Mutations = adenomatous polyposis coli (APC) gene on chromosome 5
- Site of polyps = colon (most common), followed by small bowel, and gastric polyps.
- Classic FAP:
 - > 100 colonic adenomas required for diagnosis (average 500 – 2500 adenomas)
 - 100% risk of progression into colon cancer.
- Attenuated FAP:
 - Average of 30 polyps, mostly in proximal colon.
 - 50% risk of progression into colon cancer.

(ii). Extra-intestinal Features:

- Congenital hypertrophy of retinal pigment epithelium (CHRPE) – 70–80%
- **Gardner syndrome** = FAP plus osteomas, epidermal cysts, fibromatosis.
- **Turcot syndrome** = FAP plus CNS tumors.
- Benign osteomas (especially skull & angle of mandible)

(iii). Management:

- Start screening with sigmoidoscopy at age of 12, every year.
- In families with known FAP, at-risk family members should undergo direct mutation testing at 13 – 14 years of age.
- Treatment of choice is total procto-colectomy with ileal pouch–anal anastomosis.
- Periodic upper GI endoscopy to detect duodenal adenomas.

B. Hereditary Non-polypsis Colorectal Cancer (HNPCC):

- Also known as Lynch Syndrome.
- Inheritance = autosomal dominant
- Mutations in DNA repair genes, leading microsatellite instability.
- It is responsible for 5 – 10% of colon cancer
- **Modified Amsterdam-II diagnostic criteria:**
 1. ≥ 3 relatives with colon cancer (at least 1 first-degree relative).
 2. ≥ 2 generations with colorectal cancer.
 3. At least 1 member affected is under 50 years of age.
 4. FAP excluded.
- Increased risk for endometrial and ovarian cancer.

Colon Adenocarcinoma:

I. Introduction:

- **Risk Factors:**
 - Dietary Factors:
 - Low-fiber diet.
 - High red meat
 - High animal saturated fat consumption
 - Decreased calcium (because it binds & precipitates fecal bile acids)
 - Non-dietary Factors:
 - Age older than 50 years
 - Cigarette smoking
 - Familial adenomatous polyposis (FAP)
 - Hereditary non-polypsis colorectal cancer (HNPCC)
 - IBD (Ulcerative colitis >> Cohn's disease)
 - Cholecystectomy (effect of bile acids in right colon)
- **Genetics:**
 - Most cases are sporadic
 - Colon cancers mostly arise from malignant transformation of an adenomatous polyp.
 - **The adenoma-carcinoma sequence** consists of following steps:

(Mnemonic – “AK – 53”)

- Step 1 (Knudson’s two-hit hypothesis)
 - Early adenoma = **APC gene (earliest change)** affected
 - First hit = patients born with one mutant allele of APC
 - Second hit = loss of normal copy of APC gene follows.
- Step 2 = intermediate adenoma; **K-RAS gene (most frequent activated oncogene)**
- Step 3 = late adenoma; affected gene is SMAD4.
- Step 4 = carcinoma; **loss of p53 tumor suppressor gene.**
- Increased telomerase activity (making cells immortal)
- **Locations:**
 - Rectosigmoid colon (most common)
 - Ascending colon
 - Descending colon
 - Transverse colon and cecum.
- **Clinical Features:**
 - Left-sided Cancer:
 - Bowel diameter is smaller than right colon, therefore tumor tends to obstruct.
 - It presents as circumferential growth producing “napkin-ring” configuration.
 - It causes obstruction, altered bowel habits (constipation and diarrhea), tenesmus, **bright red blood coats the stool.**
 - Lesser microsatellite instability.
 - Right-sided Cancer:
 - Bowel diameter is greater than left colon, therefore tumor tends to bleed.
 - It presents as polypoid mass.
 - It causes melena (bloody stools) and iron-deficiency anemia, mass in RIF, **blood is mixed with stool.**
 - Greater microsatellite instability.

II. Diagnosis & Management:

- **Diagnosis:**
 - Fecal occult blood test
 - **Colonoscopy with biopsy (gold standard)**
 - Barium enema
 - DNA testing (if familial polyposis)
 - Serum **carcinoembryonic antigen (CEA)** is used to detect recurrence.

▪ **Metastasis:**

- Regional lymph nodes (most common)
- Distant Metastasis:
 - Liver (most common)
 - Lungs
 - Bones
 - Peritoneal cavity

▪ **Duke's Staging:**

- Stage A = tumor invasion confined to the bowel wall.
 - Prevalence at diagnosis = 10%
 - 5 – year survival rate = > 90%
- Stage B = tumor invades through the bowel wall, but not involving lymph nodes
 - Prevalence at diagnosis = 35% (most common)
 - 5 – year survival rate = 65%
- Stage C = tumor involves the lymph nodes.
 - Prevalence at diagnosis = 30%
 - 5 – year survival rate = 30 - 35%
- Stage D = distant metastasis (e.g. liver involvement)
 - Prevalence at diagnosis = 25%
 - 5 – year survival rate = < 5%

R_x

Treatment:

- Surgical resection with lymphadenectomy is the only curative treatment.
- Two-thirds of patients have lymph node or distant metastasis at presentation and are, therefore beyond cure with surgery alone.
- Adjuvant chemotherapy with 5-fluorouracil and folinic acid for 6 months.
- Pre-operative radiotherapy for large, fixed cancers.

▪ **Screening for Colon Cancer:**

- No family history = colonoscopy every 10 years beginning at age 50.
- HNPCC = colonoscopy starting at age 25 years, every 1 – 2 years.
- Family History of Colon Cancer

Screening in Patients with Family History of Colon Cancer

<u>Category</u>	<u>Screening</u>
1 First-degree relative < 60 years old with: Colon Cancer – OR: Adenomatous polyp	<ul style="list-style-type: none"> ▪ Timing: <ul style="list-style-type: none"> ○ Age = 40 – OR: ○ 10 years earlier than the age at which the affected member developed cancer ▪ Method – Colonoscopy x 5 yearly
≥ 2 first-degree relatives at any age with: Colon Cancer – OR: Adenomatous polyp	
1 first-degree relative > 60 years old with: Colon Cancer – OR: Adenomatous polyp	<ul style="list-style-type: none"> ▪ Timing – Age = 40 ▪ Method: <ul style="list-style-type: none"> ○ Colonoscopy x 10 yearly – OR ○ Flexible sigmoidoscopy x 5 yearly – OR ○ Double contrast barium enema x 5 yearly
≥ 2 “second”-degree relatives at any age with: Colon Cancer – OR: Adenomatous polyp	

Diverticulosis (Diverticular Disease):

I. Introduction:

- It refers to acquired outpouchings of colonic mucosa through the colonic wall.
- It is "false diverticula" as it only contains mucosa and submucosa.
- **Sites:**
 - Left-side > right side of colon
 - Sigmoid colon – most common
 - Descending colon
 - Right-side > left side of colon in Asians
 - Cecum
 - Entire colon
- **Risk Factors:**
 - Low fiber diet
 - Chronic constipation
 - Family history
 - Ageing

II. Clinical Features:

- Age = > 70 years
- Asymptomatic in majority of cases.
- Colicky pain in the left iliac fossa, as a result of constipation.
- Complications:
 - **Diverticulitis:**
 - It refers to inflammation of one or more diverticula.
 - It is the most common complication of diverticular disease.
 - Clinical Features:
 - Lower abdominal pain, usually in the left iliac fossa.
 - Tenderness in left iliac fossa.
 - Sigmoid colon is often palpable, tender, thickened.
 - Fever, nausea, vomiting, and altered bowel habits.
 - Also known as "**left-sided appendicitis**".
 - Other Complications:
 - Peritonitis
 - Intestinal obstruction
 - Hemorrhage
 - Fistula formation:
 - **Vesicocolic fistula (i.e. with bladder) = most common**
 - **Vaginocolic fistula**

III.

R_x

Management:

■ Diagnosis:

- Diverticulosis:
 - Colonoscopy – investigation of choice
 - Barium enema – confirms diagnosis
- Diverticulitis:
 - CT scan – investigation of choice
 - **Colonoscopy and barium enema are contraindicated due to risk of perforation.**
 - **Colonoscopy should be done 6 weeks post attack to rule out malignancy.**

■ Treatment:

- Diverticulosis:
 - Asymptomatic = no treatment
 - Constipation:
 - High fiber diet
 - Bulk-forming Laxatives – ispaghula, methylcellulose
 - Avoid stimulant laxatives – bisacodyl, docusate, senna
- Diverticulitis:
 - Mild Attack:
 - Treatment is done on outpatient basis.
 - Antibiotics that cover E. coli and anaerobes i.e.
 - Ciprofloxacin + Metronidazole – 7-10 days – OR:
 - Co-amoxiclav + Metronidazole – 7-10 days
 - Severe Attack (cannot take orally):
 - Admit the patient.
 - NPO
 - IV fluids
 - IV antibiotics (gram-negative & anaerobic coverage)
 - Abscesses > 4 cm should be drained – surgically or percutaneously
 - Diet:
 - Low-fiber diet immediately after acute episode
 - High-fiber diet when > 6 weeks without symptoms
 - Surgery:
 - Failure of medical therapy
 - Undrainable abscess
 - Free perforation
 - Recurrent disease (≥ 2 severe episodes)

Hirschsprung's Disease:

I. Introduction:

- It is also known as "congenital aganglionic megacolon".
- It is characterized by congenital absence of ganglion cells and ganglia in the muscle wall and submucosa of the affected segment.
- It is due to lack of both Meissner's submucosal and Auerbach's myenteric plexuses.
- The affected portion of gut is tonically contracted causing functional obstruction.
- The normal proximal portion of gut becomes progressively distended due to buildup of fecal matter.
- **Types:**
 - Short-segment disease:
 - It is the most common type.
 - Involves only rectum and sigmoid.
 - More common in males.
 - Long-segment disease:
 - It is less common.
 - Involves the entire colon.
 - More common in females.

II. Clinical Features & Management:

- **Presentation:**
 - Delayed passage of meconium
 - Constipation
 - Abdominal distention
 - Vomiting
 - Rectum is empty on digital examination.
 - Associations:
 - Down syndrome = 10%
 - Neurologic deficits = 5%
 - Major complications:
 - Superimposed enterocolitis
 - Perforation of colon with peritonitis
- **Management:**
 - Investigation of choice = rectal biopsy (full-thickness biopsy)
 - Anorectal manometry = failure of rectum to relax with balloon distension
 - Treatment of choice = surgical resection of affected segment.

▪ **Acquired Megacolon:**

- Chagas disease – trypanosomes invade bowel wall and destroy enteric plexuses
- Malignancy
- Toxic megacolon (ulcerative colitis or Crohn's disease)
- Functional psychosomatic disorder

Acute Pseudo-Obstruction:

I. Introduction:

- Definition – it refers to loss of intestinal peristalsis in the absence of mechanical obstruction.
- **“Ogilvie’s syndrome”** – it refers to acute colonic pseudo-obstruction, in the presence of competent ileo-cecal valve.
- Risk Factors:
 - Surgery (abdominal)
 - Severe medical illness – sepsis
 - Intestinal ischemia
 - Medications – opiates, anti-cholinergics
 - Electrolyte abnormalities – hypokalemia, hyperkalemia, hypomagnesemia

II. Diagnosis & Management:

▪ **Clinical Features:**

- Abdominal discomfort
- Abdominal distention, nausea, vomiting,
- No peritoneal signs – (unless perforation)
- Bowel sounds – normal – high-pitched (initially)

▪ **Diagnosis:**

- Imaging (CT, X-ray):
 - Gas-filled loops of small & large bowel
 - **Cecal diameter > 10 cm is associated with increased risk of perforation**
 - In mechanical obstruction there will be absence of gas in rectum
- Treatment:
 - NPO
 - Mobilize the patient
 - Treat underlying condition
 - Colonic decompression – rectal tube, sigmoidoscopy, colonoscopy
 - Medications:
 - Ogilvie’s syndrome = neostigmine (anti-cholinesterase)
 - Small bowel = methyl-naltrexone

Pancreatic Disorders

Pancreatitis:

I. Acute Pancreatitis:

- It refers to acute inflammation of the pancreas.
- **Causes:** (mnemonic **GET SMASHED**):
 - Gallstones (most common)
 - Ethanol (alcohol)
 - Trauma
 - Steroids
 - Mumps
 - Autoimmune
 - Scorpion venom
 - Hyperlipidemia
 - Endoscopy (ERCP)
 - Drugs:
 - Thiazide diuretics
 - Azathioprine
- **Pathogenesis:**
 - It results from auto-digestion of pancreatic substance by inappropriate activation of pancreatic enzymes.
 - Activation of trypsinogen is an important triggering event in acute pancreatitis.
 - Activated enzymes cause:
 - Interstitial inflammation and edema.
 - Proteolysis (proteases)
 - Fat necrosis (lipase and phospholipase)
 - Hemorrhage (elastase)
- **Clinical Features:**
 - Symptoms:
 - Severe, constant abdominal pain (cardinal manifestation)
 - Pain radiates to back with epigastric tenderness
 - Sitting forward may relieve pain.
 - Nausea and vomiting
 - Signs:
 - Fever and tachycardia
 - Jaundice
 - Peri-umbilical discoloration (**Cullen's sign**)
 - Flank discoloration (**Grey Turner's sign**)

Investigations:

- Elevated serum amylase in the first 24 hrs (> 1000 U/mL)
- Elevated serum lipase (more sensitive & specific)
- Contrast-enhanced CT scan – best imaging study.
- Abdominal X-ray:
 - **Sentinel Loop Sign** = dilated proximal jejunum near pancreas.
 - **Colon Cut-off Sign** = dilated colon to mid-transverse colon & no air distally.

Clinical Pearl:

Serum Amylase:

- Serum amylase levels > 3 times the upper normal limit is suggestive of pancreatitis.
- Serum amylase can be elevated in conditions other than acute pancreatitis.
- Mnemonic: **TUMER**:
 1. Torsion of intra-abdominal viscus
 2. Upper GI-perforation
 3. Mesenteric infarction
 4. Ectopic pregnancy
 5. Retroperitoneal hematoma

Complications:

- Systemic organ failure
- Disseminated intravascular coagulation (DIC)
- Pancreatic abscess
- Pancreatic pseudocyst
- Chronic pancreatitis



Treatment:

- Nothing per oral (NPO)
- Fluid resuscitation
- Monitoring of vital signs, central venous pressure, urine output and blood gases.
- Nutrition:
 - Enteral route is preferred over parenteral feeding.
 - Nasogastric tube can be used as it appears to be effective in 80% cases.
- Analgesia (IV meperidine, or morphine)
- Antibiotics
- If the cause is suspected of biliary origin:
 - Emergency ERCP with biliary sphincterotomy
 - It is best undertaken within 72 hours of onset.
 - Cholecystectomy should be undertaken within 2 weeks following resolution of pancreatitis – and preferably during the same admission.

II. Chronic Pancreatitis:

Causes:

- Alcohol (most common)
- Pancreatic duct obstruction
- Hereditary pancreatitis
- Neoplasms

Clinical Features:

- Abdominal pain; it is recurrent and severe.
- Abdominal pain is located in epigastrium and radiates to back.
- Skin pigmentation over the abdomen and back is common.
- Endocrine insufficiency – diabetes mellitus:
 - Overall 30% patients are diabetic.
 - In chronic calcific pancreatitis 70% are diabetic.
- Exocrine insufficiency:
 - Anorexia and weight loss (due to protein malabsorption)
 - Steatorrhea (due to fat malabsorption) – occurs when > 90% of exocrine tissue has been destroyed.

Investigations:

- Ultrasound
- Abdominal X-ray = pancreatic calcifications
- ERCP (endoscopic retrograde cholangiopancreatography):
 - **Dilated Chain of Lakes** i.e.
 - Sacculations with intervening short strictures.

Rx

Treatment:

- Avoid alcohol
- Pain control:
 - NSAIDs
 - Opiates
 - Celiac plexus neurolysis
 - Minimally invasive thoracoscopic splachnicectomy
- Malabsorption:
 - Dietary fat restriction
 - Pancreatic enzyme replacement

III. Pancreatic Pseudocyst:

- It refers to localized collections of necrotic-hemorrhagic material rich in pancreatic enzymes.
- It is called “pseudo”, because it lacks an epithelial lining and the wall is formed by granulation tissue.
- It is the most common pancreatic cyst (75%).
- **Causes:**
 - Acute pancreatitis – mostly after 4 weeks.
 - Chronic pancreatitis – 10% of patients.
 - Abdominal trauma.
- **Treatment:**
 - Indications:
 - Pseudocysts that are large and thick-walled (> 6cm)
 - Pseudocysts that have lasted from > 6 weeks.
 - Treatment Options:
 - Percutaneous approach – percutaneous transgastric cystogastrostomy.
 - Surgical approach

Pancreatic Tumors:

I. Insulinoma:

- Also known as "beta cell tumor".
- It is the most common islet cell tumor.
- It produces insulin.
- **Clinical Findings:**
 - **Whipple Triad:**
 - Episodic hypoglycemia (from increased insulin).
 - CNS dysfunction (confusion, anxiety, stupor, coma)
 - Dramatic reversal of symptoms by glucose intake.
- **Lab Findings:**
 - Elevated insulin
 - Decreased glucose
 - No ketoacidosis
 - C-peptide:
 - It is elevated in insulinoma.
 - It is not elevated in exogenous insulin intake.

II. Gastrinoma:

- Also known as "G-cell tumor".
- It is often a malignant tumor and sometimes occurs in extra-pancreatic sites.
- It produces gastrin.
- It is associated with MEN-I (multiple endocrine neoplasia-I).
- It is associated with **Zollinger-Ellison Syndrome**

III. Pancreatic Carcinoma:

- It is a common tumor accounting for $\leq 2\%$ of all malignancies.
- It is most common adenocarcinoma (90%).
- Age = 60 – 80 years
- **Risk Factors:**
 - Smoking
 - High fat consumption
 - Chronic pancreatitis
 - Diabetes mellitus

▪ Mutations:

- Early Stage = K-RAS gene is the **most common affected oncogene**
- Intermediate Stage = p-16 gene is the **most common affected tumor suppressor gene**
- Late Stage:
 - Inactivation of tumor suppressor genes p53 (50-70%) and SMAD4 (55%).
 - Inactivation of tumor suppressor gene BRCA2

▪ Location:

- Head (60%)
- Body (15%)
- Tail (5%)
- Entire gland (20%)

▪ Clinical Presentation:

- Painless obstructive jaundice (carcinoma of head)
- Epigastric pain (carcinoma of body and tail)
- Anorexia
- Weight loss
- Palpable non-tender gallbladder (**Courvoisier's Sign**)
- Carcinoma of Head of Pancreas:
 - Produces symptoms early; most develop jaundice.
 - Because it obstructs the common bile duct & causes distension of the biliary tree
- Carcinoma of Body & Tail:
 - Produces no symptoms; remains silent until advanced.
 - Because they don't impinge on biliary tract.

Chapter 10

HEPATOLOGY

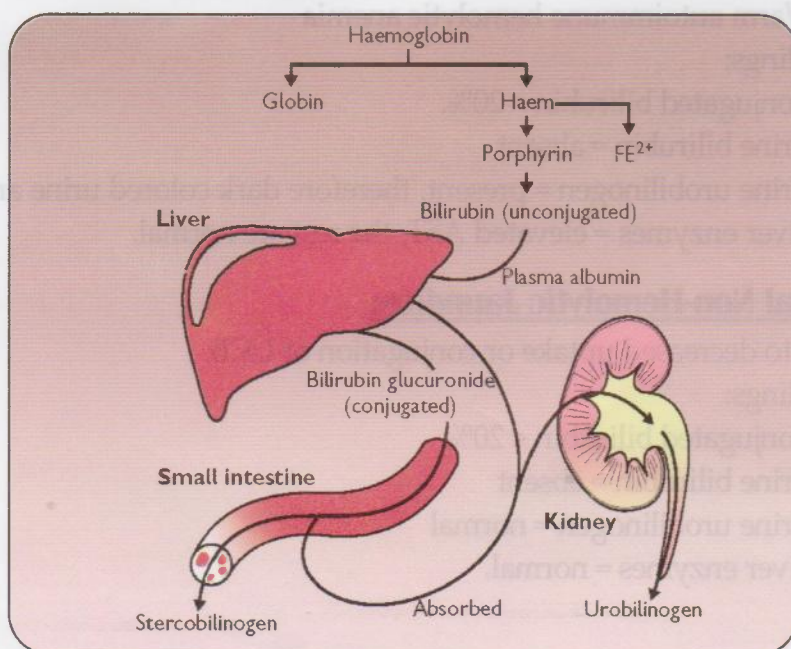


Jaundice

- Jaundice refers to yellow discoloration of skin, sclera, and mucous membranes.
- Jaundice results from an increased bilirubin concentration in the body fluids.
- Jaundice is usually detectable clinically when the plasma bilirubin exceeds $40 \mu\text{mol/l}$ (2.5 mg/dL)

Bilirubin Metabolism:

- **Unconjugated Bilirubin (UCB):**
 - Also known as "indirect bilirubin". It is lipid soluble.
 - It is the end-product of heme degradation.
 - It binds to albumin and is transported from blood to liver hepatocytes.
 - It is bound to albumin, therefore cannot be excreted in the urine even when blood levels are high.



▪ **Conjugated Bilirubin (CB):**

- Also known as "direct bilirubin". It is water soluble.
- It formed when UCB is conjugated by hepatic UDP-glucuronyltransferase (UGT1A1).
- Being water soluble and only loosely bound to albumin excess CB in plasma can be excreted in urine.
- It is stored in gallbladder; and released into duodenum via common bile duct.
- It is converted to urobilinogen by the intestinal bacteria.

▪ **Urobilinogen:**

- 80% of urobilinogen is converted to urobilin, and excreted in feces.
- 20% of urobilinogen is recycled to liver (90%) and kidneys (i.e. in urine (10%)).

I. Unconjugated Hyperbilirubinemia:

- It is a type of jaundice in which conjugated bilirubin is < 20%.
- It is of two types:
 - Hemolytic jaundice
 - Congenital non-hemolytic jaundice

(i). Hemolytic Jaundice:

- It is due to increased production of unconjugated bilirubin (UCB).
- It is caused by extra-vascular hemolytic anemias:
 - Hereditary spherocytosis
 - Sickle cell anemia
 - Hemolytic disease of newborn
 - Warm autoimmune hemolytic anemia
- Lab Findings:
 - Conjugated bilirubin < 20%.
 - Urine bilirubin = absent
 - Urine urobilinogen = present, therefore dark colored urine and stool
 - Liver enzymes = elevated AST; the rest are normal.

(ii). Congenital Non-Hemolytic Jaundice:

- It is due to decreased uptake or conjugation of UCB.
- Lab Findings:
 - Conjugated bilirubin < 20%.
 - Urine bilirubin = absent
 - Urine urobilinogen = normal
 - Liver enzymes = normal.

(i). Crigler-Najjar Syndrome-I:

- Autosomal recessive; **UGT1A1 activity = absent.**
- Liver = normal
- Clinical Features:
 - Rapid rise of indirect bilirubin in first days of life (>20 mg/dL)
 - **Fatal in infancy secondary to kernicterus**
 - Treatment:
 - Intensive phototherapy
 - Exchange transfusion
 - Liver Transplantation

(ii). Crigler-Najjar Syndrome-II:

- Autosomal dominant; **UGT1A1 activity = decreased**
- Liver = normal
- Clinical Features:
 - It caused mild jaundice compared to type-I
 - Kernicterus is NOT common.
 - Treatment = oral phenobarbital

(iii). Gilbert Syndrome:

- Autosomal dominant; UGT1A1 activity = decreased
- Liver = normal
- Clinical Features:
 - Benign disorder; requires no treatment.
 - Bilirubin unlikely to be elevated more than 5 mg/dL.
 - It presents in adolescents or adult life.
 - Jaundice occurs in response to triggers such as:
 - Alcohol; **Fasting**
 - Strenuous exercise; Intercurrent illness
 - Rx – no treatment necessary

III. Hepatocellular Jaundice:

- It results from inability of the liver to transport bilirubin into the bile, as a consequence of parenchymal liver disease.
- It causes a mixed hyperbilirubinemia i.e. elevation of both UCB and CB.
- Lab Findings:
 - Conjugated bilirubin = 20 – 50%.
 - Urine bilirubin = increased
 - Urine urobilinogen = increased
 - Liver enzymes:

- Viral hepatitis = ALT > AST, mild elevation of ALP and GGT.
- Alcoholic hepatitis = AST > ALT, mild elevation of ALP and GGT.

IV. Cholestatic (Obstructive) Jaundice:

- It is conjugated hyperbilirubinemia and results from:
 - Conjugated bilirubin cannot enter bile canaliculi and passes back into the blood.
 - Failure of clearance of unconjugated bilirubin arriving at the liver.
- Causes:
 - Decreased intra-hepatic bile flow:
 - Drug induced (e.g. oral contraceptives)
 - Primary biliary cirrhosis
 - Autoimmune hepatitis
 - Congenital conjugated hyperbilirubinemia.
 - Rotor's syndrome
 - Dubin – Johnson syndrome

<u>Congenital Conjugated Hyperbilirubinemia</u>		
	<u>Pathology</u>	<u>Management</u>
Dubin – Johnson	Autosomal Recessive Decreased canalicular excretion of bilirubin	Mild Jaundice No treatment necessary
Rotor's syndrome	Autosomal Recessive Decreased bilirubin uptake & intra-hepatic binding	Mild Jaundice No treatment necessary

- Decreased extra-hepatic bile flow:
 - Choledocholithiasis; Carcinoma of head of pancreas
 - Parasitic infestation; Biliary strictures
- Lab findings:
 - Conjugated bilirubin = > 50%.
 - Urine bilirubin = increased
 - Urine urobilinogen = absent
 - Liver enzymes:
 - Mild elevation of ALT and AST
 - **Marked elevation of ALP and GGT**

**Clinical Pearl:****Obstructive Jaundice:**

- **Clinical Features & Complications:**

- Early Features:

- Jaundice, Pruritus
 - Dark urine, Pale stools

- Late Features:

- Xanthelasma & xanthomas
 - Malabsorption:
 - Fat soluble vitamin deficiency – A, D, E, K
 - Weight loss, Steatorrhea, Osteomalacia, Bleeding Tendency

Hyperbilirubinemia (Jaundice)

Type of Jaundice	Unconjugated	Hepatocellular	Obstructive
Causes	Hemolytic jaundice Congenital non-hemolytic	Hepatitis (viral)	Decreased intra-hepatic & extra-hepatic bile flow
CB	< 20%	20 – 50%	> 50%
Urine bilirubin	Absent	Increased	Increased
Urine urobilinogen	Increased = hemolytic (dark urine & stool) Normal = congenital	Normal	Absent (pale stool & urine)
AST	Increased = hemolytic Normal = congenital	Marked elevation	Mild elevation
ALT	Normal	Marked elevation	Mild elevation
ALP	Normal	Mild elevation	Marked elevation
GGT	Normal	Mild elevation	Marked elevation



Clinical Pearl:

LFT Part-I: Transaminases:

- Alanine Transaminase (ALT):
 - It is present in cytosol; it is specific enzyme for liver cell necrosis.
 - Viral hepatitis = ALT >> AST.
- Aspartate Transaminase (AST):
 - is present in mitochondria
 - Alcoholic hepatitis = AST >> ALT (because alcohol is mitochondrial toxin)

LFT Part-II: Cholestatic Jaundice:

- Cholestatic jaundice is characterized by
 1. Conjugated hyperbilirubinemia
 2. Elevated alkaline phosphatase (ALP)
 3. Elevated gamma glutamyltransferase (GGT).
- Alkaline Phosphatase (ALP):
 - It is present in bile duct epithelium and canalicular membrane of hepatocytes.
 - Its elevation is characteristic of cholestatic jaundice.
- Gamma Glutamyltransferase (GGT):
 - It is raised in intrahepatic and extrahepatic obstruction to bile flow.
 - Increased ALP, but normal GGT = source other than bones)
 - Increased ALP and GGT = cholestatic jaundice.

GGT	Normal	Mild elevation	Marked elevation
ALP	Normal	Mild elevation	Marked elevation
ALT	Normal	Mild elevation	Marked elevation
AST	Normal - conjugated	Increased - hepatocytic	Marked elevation - hepatocytic

Cirrhosis & Its Complications

Cirrhosis:

I. Introduction:

- It is end-stage liver disease characterized by **irreversible “diffuse” fibrosis** with formation of regenerative nodules.
- Decompensated cirrhosis refers to cirrhosis in association with jaundice, variceal hemorrhage, ascites, or encephalopathy.
- Cirrhosis is the most common cause of portal hypertension.

▪ Causes:

- **Viral hepatitis (hepatitis B and C) – most common cause worldwide**
- **Alcoholic liver disease (most common) – most common cause in the West.**
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune hepatitis
- Hemochromatosis
- Wilson disease
- α 1-antitrypsin deficiency
- cryptogenic cirrhosis (non-alcoholic fatty liver disease) – 10-15%

▪ Clinical Presentation:

- Asymptomatic
- Anorexia, weight loss
- Jaundice, coagulopathy, encephalopathy
- Portal hypertension (ascites, esophageal varices)
- Signs:
 - Liver:
 - Initially=enlarged, firm, palpable (predominantly left lobe)
 - Eventually=shrunken and nodular
 - Signs of Compensate Cirrhosis:
 - Xanthothesma; parotid enlargement
 - Spider angiomas and palmar erythema (due to increased estrogen)
 - Enlargement of parotid and lacrimal glands
 - Gynecomastia; testicular atrophy
 - Splenomegaly; liver (small or large)
 - Purpura and pigmented ulcers; clubbing

- Signs of Decompensated Cirrhosis:

- Encephalopathy
- Asterixis (flapping tremors),
- Ascites; caput medusae
- Edema; Feter hepaticus

- Signs of portal HTN:

- Splenomegaly, ascites,
- Caput medusae (dilated superficial abdominal veins)
- Esophageal varices

II. Investigations:

- **Severity of Disease:**

- Liver function:

- Serum albumin & prothrombin time (PT) are best indicators of liver function.

- Poor prognosis = decreased serum albumin (< 28 g/L) & increased PT.

- LFTs:

- Elevated bilirubin
 - Elevated aminotransferases (ALT & AST)
 - Elevated serum ALP.

- Serum electrolytes = hyponatremia (low serum sodium)

- Serum creatinine = elevated concentration of > 130 $\mu\text{mol/L}$ is marker of worse prognosis.

- CBC (anemia, leucopenia, thrombocytopenia)

- **Cause of Disease:**

- Viral markers (for hepatitis B, C)
 - Serum autoantibodies (for autoimmune hepatitis)
 - Serum immunoglobulins
 - Iron profile and ferritin (for hemochromatosis)
 - Copper and ceruloplasmin (for Wilson's disease)
 - α -1 anti-trypsin levels

- **Imaging:**

- Abdominal ultrasound
 - CT scan abdomen
 - Endoscopy – for detection of varices and hypertensive gastropathy
 - MRI – for diagnosis of benign tumors
 - Liver Biopsy – to confirm the severity and type of liver disease.

▪ **Prognosis of Cirrhosis:**

Child – Pugh Classification of Prognosis in Cirrhosis

Score	1	2	3
Ascites	None	Mild	Marked
Encephalopathy	None	Mild	Marked
Bilirubin ($\mu\text{mol/L}$)	< 34	34 – 50	> 50
Albumin (g/L)	> 35	28 – 35	< 28
PT (seconds over normal)	< 4	4 – 6	> 6

Add above scores to your patient for survival figures below.

To convert bilirubin in $\mu\text{mol/L}$ to mg/dL , divide by 17.

Grade	1-year survival	5-year survival	10-year survival
Child's A (< 7)	82	45	25
Child's B (7 – 9)	62	20	7
Child's C (≥ 10)	42	20	0

Clinical Pearl:

Poor Prognostic Indicators In Cirrhosis:

1. Low albumin (< 28 g/L)
2. Low serum sodium (< 125 mmol/L)
3. Prolonged PT (> 6 seconds above normal value)
4. Raised creatinine (> 130 $\mu\text{mol/L}$)
5. Clinical Factors:
 - Persistent jaundice
 - Failure to respond to therapy
 - Ascites; Variceal hemorrhage
 - Encephalopathy; Small liver
 - Persistent hypotension

▪ **Complications of Cirrhosis:**

- Ascites
- Portal hypertension
- Progressive heart failure
- Hepato-renal syndrome
- Hepato-pulmonary syndrome
- Spontaneous bacterial peritonitis
- Hepatocellular carcinoma



Clinical Pearl: Management of Cirrhosis:

- There is no specific management for cirrhosis.
- The basic principle of management are:
- Treatment of underlying cause.
- Prevention and treatment of complications
- Liver transplantation

Complications of Cirrhosis:

I. Portal Hypertension:

- Portal vein is formed by the union of superior mesenteric vein and splenic vein.
- Portal venous pressure is normally 5 – 8 mmHg.
- Clinical features and complications of portal HTN when portal venous pressure is > 12 mmHg.
- **Definition: hepatic venous pressure gradient (HVPG) of > 5 mmHg.**
- **Types:**
 - Pre-Hepatic Pre-sinusoidal: (due to blockage of portal vein before the liver):
 - Portal vein thrombosis
 - Splenic vein thrombosis
 - Intra-Hepatic Causes:
 - Pre-sinusoidal = schistosomiasis, sarcoidosis, drugs, primary biliary cirrhosis
 - Sinusoidal = **cirrhosis (most common)**, metastatic malignant disease
 - Post-sinusoidal = veno-occlusive disease
 - Post-Hepatic Post-Sinusoidal Causes (due to venous blockage outside the liver)
 - Budd-Chiari syndrome
 - Right-side HF; Constrictive pericarditis
- **Clinical Features:**
 - Splenomegaly:
 - **It is the cardinal finding.**
 - Splenomegaly is marked in childhood and adolescence.
 - Splenomegaly in adults, however, is rarely more than 5 cm.

- Ascites:
 - It is present with post-hepatic and sinusoidal portal HTN.
 - It is not seen in pre-sinusoidal portal HTN.
- Fetor Hepaticus:
 - Also known as **"Breath of the Dead"**.
 - It is the characteristic smell of breath in cirrhosis, due to portosystemic shunting of blood, which allows "mercaptans" to pass directly to lungs.
- Caput medusae
- **Cruveilhier – Baumgarten syndrome** – venous hum on auscultation from distention of para-umbilical veins.
- Complications:
 - Ascites
 - Variceal bleeding – most important clinical feature
 - Hypersplenism (causing thrombocytopenia)
 - Congestive gastropathy
 - Hepatic encephalopathy
 - Renal failure

II. Ascites:

- It refers to accumulation of excess fluid in the peritoneal cavity.
- It becomes clinically detectable when at least 500 mL has accumulated.
- **Pathogenesis:**
 - Sinusoidal hypertension (i.e. portal hypertension)
 - Hypoalbuminemia (causes decreased plasma oncotic pressure and transudation of fluid)
 - Percolation of hepatic lymph into peritoneal cavity
 - Splanchnic vasodilation (intestinal fluid leakage)
 - Secondary hyperaldosteronism (increased renal retention of sodium and water)
- **Signs:**
 - Abdominal distension
 - Fluid thrill and shifting dullness to percussion.

R_x

Management:

- Sodium and Water restriction:
 - Restriction of sodium intake to 100 mmol/day i.e. "no added salt diet"
 - Restriction of water to 1 – 1.5 L/day only when serum sodium is < 125 mmol/L.
- Diuretics:
 - **Spironolactone (aldosterone antagonist) is the drug of choice.**
 - Spironolactone (100 – 400 mg/day) can be combined with a loop diuretic i.e. furosemide.
 - Spironolactone is associated with gynecomastia and hyperkalemia.
 - **Refractory Ascites (Diuretic – resistant Ascites):**
 - It refers to ascites in which the patients do not respond to doses of 400 mg spironolactone and 160 mg furosemide.
- Treatment of Refractory Ascites:
 - Large-volume paracentesis:
 - **It is the first-line treatment of refractory ascites.**
 - Remove 3 – 5 L per day or until dry.
 - Albumin replacement (6 – 8 gm per litre of ascites removed) to support circulation.
 - It must not be performed in the presence of spontaneous bacterial peritonitis (SBP) as it increases the risk for acute renal failure.
 - Trans-jugular intra-hepatic portosystemic shunt (TIPSS)
 - It is also used for refractory ascites.
 - It does not improve mortality, but increases the risk for encephalopathy.

Causes of Ascites

<u>Portal HTN-related Ascites</u> <u>SAAG ≥ 1.1 g/dL</u>	<u>Non-portal HTN-related Ascites</u> <u>SAAG < 1.1 g/dL</u>
<ol style="list-style-type: none"> 1. Cirrhosis 2. Acute hepatitis 3. Liver malignancy 4. Right-sided HF 5. Budd-Chiari syndrome 6. Splenic vein thrombosis 7. Schistosomiasis 	<ol style="list-style-type: none"> 1. Peritonitis (e.g. tuberculosis) 2. Peritoneal Carcinomatosis 3. Pancreatitis 4. Vasculitis 5. Hypoalbuminemia (nephrotic syndrome) 6. Meig's syndrome (ovarian tumor) 7. Hypothyroidism

▪ Exudative & Transudative Ascites:

- SAAG stands for serum albumin – ascitic fluid gradient.
- **SAAG = (Serum Albumin) – (Albumin level of Ascitic Fluid)**
- SAAG is helpful in distinguishing ascites secondary to portal HTN from ascites not related to portal HTN.
- Exudative ascites occurs when total protein concentration is $> 25\text{g/L}$ and SAAG is $< 1.1\text{ g/dL}$.
- Exudative ascites is a protein-rich and cell-rich fluid; hence, the difference between serum and ascitic fluid albumin is much less.
- Transudative ascites occurs when total protein concentration is $< 25\text{g/L}$ and SAAG is $> 1.1\text{ g/dL}$.
- Transudative ascites is a protein-poor and cell-poor fluid; hence, the difference between serum and ascitic fluid albumin is high.

III. Esophageal Varices:

- It results from portosystemic shunts, which are formed wherever systemic and portal circulation share common capillary beds.
- It presents with **hematemesis** (upper gastrointestinal bleeding) in a patient with cirrhosis.
- In esophageal portosystemic shunt is formed between:
 - It is formed between esophageal branches of left gastric vein (portal tributary).
 - Esophageal veins draining the middle-third of esophagus into azygos veins (systemic tributary)



Emergency Management:

- Assess pulse and blood pressure.
- Insert an intravenous line and obtain blood for investigations.
- Normal saline – for extracellular volume replacement.
- Terlipressin – drug to reduce portal pressure.
- Prophylactic antibiotics – reduces the risk of SBP
- Urgent endoscopy – to confirm the diagnosis.
- Endoscopic band ligation – to stop bleeding
- Proton pump inhibitors – reduces the risk of secondary bleeding from banding-induced ulceration.

▪ **Endoscopic Band Ligation & Sclerotherapy:**

○ Band Ligation:

- It is the method of choice widely used as initial treatment.
- It has lower incidence of esophageal perforation and stricture.

○ Injection Sclerotherapy:

- In this method varices are injected with a sclerosing agent.
- It is associated with higher incidence of esophageal perforation and stricture.

▪ **Pharmacologic Agent:**

○ Terlipressin is the drug of choice.

- It reduces portal pressure by releasing vasopressin (vasoconstrictor).
- It reduces mortality in the setting of acute variceal bleeding.
- 2 mg IV x 4 times daily until bleeding stops, then 1 mg x 4 times daily x 72 hours
- ALTERNATIVE AGENT – Octreotide (somatostatin analogue).

○ Uses:

- It is less useful than banding in preventing re-bleeding.
- It is useful in reducing active bleeding while endoscopy is being arranged.

○ Side Effects of terlipressin:

- Abdominal cramps; arrhythmias, increased arterial pressure.
- Potentially fatal complications – myocardial infarction, cardiac failure.

▪ **Balloon Tamponade:**

○ Indications:

- If endoscopic or pharmacologic therapy has failed.
- If there is exsanguinating hemorrhage.

○ Method:

- It employs a **Sengstaken – Blakemore tube**, possessing two balloons.
- Initially, only the gastric balloon should be inflated with 200 – 250 mL of air.
- If bleeding doesn't stop, then inflate the esophageal balloon.
- However, the esophageal balloon should be deflated for 10 minutes every 3 hours to avoid esophageal mucosal damage.
- Pressure in the esophageal balloon should not exceed 40 mmHg.

- Complications:
 - Esophageal perforation
 - Aspiration pneumonia
- **Transjugular Intrahepatic Portosystemic Shunt (TIPSS):**
 - Indication = when bleeding cannot be stopped after two sessions of endoscopic therapy within 5 days.
 - Method:
 - It uses a stent placed between the portal vein and the hepatic vein within the liver to provide a portosystemic shunt and therefore reduce portal pressure.
 - It is carried out under radiological control via the internal jugular vein.
 - Complications:
 - Encephalopathy
 - Does not lower mortality

Clinical Pearl:

Esophageal Varices & Beta Blockers:

- Non-selective beta blockers (**propranolol**) can be used in the primary prevention of variceal bleeding (i.e. **before bleeding occurs**).
- The efficacy of beta-blockers in primary prevention is **similar to that** of prophylactic banding.
- Non-selective beta blockers have also been used in secondary prevention of variceal bleeding i.e. to prevent recurrent variceal bleeding.
- Non-selective beta blockers are of little importance in the management of acute variceal bleeding.

IV. Hepatic Encephalopathy:

- It is a neuro-psychiatric syndrome caused by cirrhosis, which progresses from confusion to coma.
- **Pathogenesis:**
 - It is reversible metabolic disorder.
 - In normal liver, nitrogenous substances produced by bacterial action in gut are metabolized and excluded.
 - In cirrhosis, nitrogenous substances cannot be metabolized, resulting in formation of neurotoxin.

- Neurotoxins act as false-neurotransmitters (e.g. gamma aminobutyric) and cause encephalopathy.

■ **Clinical Features:**

- Progressive mental status deterioration (confusion, drowsiness, aggressiveness, coma)
- Flapping tremor (Asterixis)
- Constructional apraxia (inability to draw objects such as a star)
- Hyper-reflexia; bilateral extensor plantar responses.
- EEG = diffuse slowing of normal alpha waves with eventual development of delta waves.

Clinical Grading of Hepatic Encephalopathy

Clinical Grade	Clinical Signs
Grade - 1	Poor concentration, slurred speech, slow mentation, disordered sleep rhythm
Grade - 2	Drowsy, but easily rousable, occasional aggressive behavior, lethargic
Grade - 3	Marked confusion, sleepy but responds to pain and voice.
Grade - 4	Coma (unresponsive to voice, may or may not respond to painful stimuli)

■ **Treatment:**

- Lactulose:
 - It is a laxative to reduce colon pH and limit colonic ammonia absorption.
 - Dose - 15 - 30 mL x 3 times daily
 - Titrate to 2 - 3 bowel movements/day.
- Neomycin - decreases ammonia-producing bacteria from gut.
- Rifaximin - 400mg x 3 times daily - decreased bacterial content of the bowel
- Avoid trigger factors:
 - Prevent dehydration; Relieve constipation
 - Correct electrolyte abnormalities (mainly hypokalemia)
 - Treat infection
 - Decrease dietary protein:
 - It is no longer recommended as first-line treatment.
 - **Branched-chain amino acids are preferred in CLD** - as they are metabolized by the skeletal muscles.

V. Spontaneous Bacterial Peritonitis (SBP)

- It is a serious complication of ascites with cirrhosis.
- **Clinical Features:**
 - Sudden onset abdominal pain and rebound tenderness
 - Absent bowel sounds and fever
 - Signs of cirrhosis and ascites.
 - Asymptomatic in 25% cases, therefore consider paracentesis in all hospitalized cirrhotic patients with ascites.
- **Ascitic Tap (Paracentesis):**
 - Color = cloudy
 - Neutrophil count = $> 250 \times 10^6/L$
 - Organism:
 - It is most commonly caused by 1 organism.
 - Organisms – E. coli (most common), pneumococci, streptococci
- **Management:**
 - Treatment = Cefotaxime (third-generation cephalosporin)
 - Prevention is by fluoroquinolones:
 - Norfloxacin (400 mg daily) – OR:
 - Ciprofloxacin (250 mg 12-hourly)

VI. Hepato-Renal Syndrome (HRS):

- It is defined as renal failure in patients with advanced cirrhosis and ascites.
- **Pathogenesis:**
 - It is mediated by severe renal vasoconstriction due to extreme under-filling of arterial circulation.
 - The kidney is pathologically normal.
 - It is a cause of renal failure, with pre-renal renal failure laboratory findings i.e. BUN to creatinine ratio of > 15 .
 - **Diagnostic Criteria:**
 - Cirrhosis with ascites
 - Creatinine $> 1.5 \text{ mg/dL}$
 - No improvement in Cr ($< 1.5 \text{ mg/dL}$) after:
 - Discontinuing diuretics, AND:
 - Volume expansion (1g/kg/day of albumin $\times 2$ days)
 - No shock
 - No nephrotoxic drug use
 - No organic kidney disease (e.g. glomerulonephritis) or obstruction

▪ **Types of HRS:**

○ **Type I HRS:**

- It has a rapidly progressive deterioration in circulatory and renal function.
- It has poor prognosis and is characterized by:
 - **Creatinine > 2.5 mg/dL or >1.5 x baseline value in < 2 weeks.**
 - Urine sodium excretion is < 10 mmol/day.
 - Urine to plasma osmolality ratio is > 1.5

○ **Type II HRS:**

- It has a more steady deterioration in circulatory and renal function.
- It has better prognosis.

▪ **Treatment of HRS:**

- Type – II HRS + Refractory Ascites = TIPSS
- Type – I HRS:
 - Octreotide + Midodrine + Albumin infusion + Terlipressin
 - **Definitive Treatment – Liver transplantation**
 - Hemodialysis (shouldn't be done routinely as it doesn't improve survival)

VII. Hepato-Pulmonary Syndrome (HPS):

▪ **Definition& Features:**

- Advanced cirrhosis, PLUS:
- Resistant hypoxemia ($\text{PaO}_2 < 70 \text{ mmHg}$), & intra-pulmonary vascular dilation
- Without intrinsic pulmonary disease
- Nitrous oxide (NO) overproduction is believed to be important in pathogenesis.

▪ **Clinical Features:**

- Clubbing
- Cyanosis
- **Platypnea–Orthodeoxia Syndrome:**
 - It refers to dyspnea and hypoxia occurring when a patient moves from a recumbent to an upright position.
 - It is due to intra-pulmonary shunting through direct arteriovenous communications.

▪ **Treatment:**

- No specific therapy
- **Liver transplantation = Definitive Treatment**

Hepatitis

Viral Hepatitis:

<u>Virus</u>	<u>Clinical Findings</u>
<u>Hepatitis A</u> <ul style="list-style-type: none"> ○ Agent = single-stranded RNA ○ Incubation = 2 – 6 week ○ Mode of transmission = fecal – oral 	<ul style="list-style-type: none"> ▪ No carrier state ▪ No chronic hepatitis ▪ No hepatocellular carcinoma ▪ It is common in day care centers, prisons, and travelers to developing countries. ▪ Donated blood is not screened for this virus because viremia is transient. ▪ Serology: <ul style="list-style-type: none"> ○ Active infection = Anti-HAV IgM ○ Recovery = Anti-HAV IgG (protective antibody) ▪ Treatment = supportive ▪ Prevention: <ul style="list-style-type: none"> ○ Active = vaccine ○ Passive = immune globulin ○ Vaccinate children and patients with chronic hepatitis B or C.
<u>Hepatitis B</u> <ul style="list-style-type: none"> ○ Agent = double-stranded DNA ○ Incubation = 4 – 20 weeks ○ Mode of transmission: <ul style="list-style-type: none"> ▪ Blood ▪ Sexual ▪ Pregnancy ▪ Breast feeding 	<ul style="list-style-type: none"> ▪ Carrier state (HBsAg in serum for > 6 months) ▪ Chronic hepatitis in 10% ▪ Risk for hepatocellular carcinoma ▪ Serology <ul style="list-style-type: none"> ○ Hepatitis B surface antigen (HBsAg): <ul style="list-style-type: none"> ✓ First marker – before the appearance of symptoms ✓ Chronic HBV infection is present if it persists > 6 mo. ○ HBeAg = evidence of viral replication and infectivity ○ HBV-DNA = infective particle ○ Anti-HBc(core)-IgM <ul style="list-style-type: none"> ✓ First antibody to appear ✓ Only positive antibody during “window phase” ○ Anti-HBc(core)-IgG <ul style="list-style-type: none"> ✓ Indicates previous infection (neg. HBsAg) ✓ Indicates ongoing infection (pos. HBsAg) ○ Hepatitis B surface antibody (Anti-HBs): <ul style="list-style-type: none"> ✓ Indicates resolution of acute disease. ✓ Indicates immunity (sole marker after vaccination) ▪ Prevention: <ul style="list-style-type: none"> ○ Active = recombinant vaccine ○ Passive = hyperimmune serum globulin

<u>Virus</u>	<u>Clinical Findings</u>
<u>Hepatitis C</u> 	<ul style="list-style-type: none"> Carrier state Chronic hepatitis. Risk for hepatocellular carcinoma Serology (see below) Agent = single stranded RNA Incubation = 2 – 26 week Mode of transmission: <ol style="list-style-type: none"> 1. Parenteral 2. Sexual contact
<u>Hepatitis D</u> Agent = single stranded RNA-defective virus Mode of transmission: parenteral	<ul style="list-style-type: none"> Coinfection with HBV results in fulminant hepatitis, recovery, or chronic hepatitis (less likely). Superinfection with HBV results in fulminant hepatitis, acute severe hepatitis, or chronic hepatitis (more likely)
<u>Hepatitis E</u> Agent = single stranded RNA Incubation = 2 – 8 weeks Transmission = waterborne	<ul style="list-style-type: none"> No chronic hepatitis No risk for hepatocellular carcinoma Only causes acute hepatitis Fulminant hepatitis in pregnant women.

Hepatitis B:

▪ Clinical Features:

○ Acute Infection:

- Fever; jaundice (mixed hyperbilirubinemia)
- Painful hepatomegaly
- Elevated serum transaminases (ALT >> AST)
- Followed by recovery
- Can progress to fulminant hepatitis in < 1% of cases.

○ Chronic Infection:

- Vertical Transmission (90%):
 - It means perinatally acquired from HBsAg-positive mother.
 - **It is the most common factor for progression to chronic liver disease.**
- Horizontal Transmission (10%):
 - Injection drug use
 - Infected unscreened blood products
 - Sexual
 - Tattoos/acupuncture needles

○ **Hepatocellular Carcinoma:**

- Highest risk for development of hepatocellular carcinoma are:
 - Perinatal transmission
 - Increased HBV DNA

○ **Extra-hepatic Syndromes:**

- Polyarteritis nodosa (PAN)
- Membranoproliferative glomerulonephritis
- Arthritis
- Dermatitis
- Polymyalgia rheumatica

▪ **Serologic Patterns:**

Stage	HBsAg	HBeAg	Anti-HBc	Anti-HBs
Acute infection	Positive	Positive	Positive(IgM)	Negative
Chronic infection	Positive	Positive	Positive (IgG)	Negative
Immune from previous infection	Negative	Negative	Positive	Positive
Immune from vaccination	Negative	Negative	Negative	Positive
Window period	Negative	Negative	Positive (IgM)	Negative

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Treatment:

(i). Goals of treatment: (i.e. good response to treatment is indicated by):

- Seroconversion of HBeAg (i.e. changing from positive HBeAg to negative HBeAg)
- Reduction of HBV DNA to undetectable levels by PCR
- Normalization of serum ALT levels
- Histologic improvement in inflammation and fibrosis

(ii). Indications of Treatment:

○ **Acute Hepatitis B:**

- It has only supportive treatment.
- Hospitalize if there is change in mental status or prolonged INR.
- Monitor for acute liver failure - < 1%.
- There is no role of antiviral therapy.
- Natural History:

- Full recovery - 90 – 95%.
- Chronic hepatitis - 5 – 10%
- Chronic hepatitis - 90% of child who acquired infection at birth

○ **Chronic Hepatitis B (Indications for Treatment):**

1.

- **HBeAg Positive**
- **HBV DNA (>20, 000 IU/mL) with abnormal serum ALT (> 2x normal).**
- Liver biopsy is not needed.

2.

- **HBeAg Negative**
- **HBV DNA (> 2000 IU/mL)**
- **Abnormal serum ALT (> 2x normal)– OR:**
- **Liver Biopsy – marked inflammation & fibrosis (stage ≥ 2 fibrosis)**

(iii). Anti-viral Agents:

○ **Nucleoside – Nucleotide Antiviral Agents:**

Entecavir – OR – Lamivudine:

- **These are the best first-line agents;** well-tolerated and low resistance.
- **Entecavir:**
 - It reduces serum HBV DNA more in HBeAg negative patients, than in those with HBeAg positive by 48 weeks.
 - It has anti-HIV action and is contraindicated in HIV patients who are not on an anti-retroviral therapy.
- **Tenofovir:**
 - It has similar potency to entecavir, and can be used as monotherapy.
 - It is also effective against lamivudine-resistance virus.

Lamivudine:

- It is a nucleoside analogue, which inhibits DNA polymerase and suppresses HBV DNA levels.
- It is effective in improving liver function in patients with decompensated cirrhosis and may prevent the need for liver transplantation.
- **YMDD Mutant:**

- It is viral resistance due to development of DNA polymerase mutants.
 - It occurs approximately 9 months after therapy.
 - It is characterized by a rise in viral load during treatment.
 - These viral mutants are LESS hepatotoxic than native virus.
 - In this case other anti-viral agents can be added (add on therapy)
- **Pegylated Interferon Alpha (PEG IFN α):**
- It shows the best rate of HBeAg Seroconversion; but its side effects limits its use.
 - It is most effective in those with low viral load and abnormal ALT ($> 2\times$ normal).
 - HBeAg positive = response rate is higher
 - HBeAg negative = response rate is lower.
 - Side Effects:
 - Acute flu-like illness
 - Headaches, myalgias, depression
 - Reversible hair loss, bone marrow suppression
 - **Contraindicated in the presence of cirrhosis** (precipitates liver failure)
- **Liver Transplantation:**
- It is an acceptable treatment option.
 - Post-transplant Prophylaxis:
 - This is very critical to prevent re-infection of transplanted liver.
 - Agents:
 - Hepatitis B Immunoglobulin, PLUS:
 - Nucleoside-Nucleotide antiviral agents
 - It has reduced reinfection rate to $< 10\%$.
 - It has increased 5-year survival to 80%.

Hepatitis C:

■ Clinical Features:

○ Acute Infection:

- 80% is subclinical,
- Only 10 – 20% is symptomatic; presenting with:
 - Hepatitis with jaundice
 - Fulminant hepatitis (very rare)

○ Chronic Infection:

- Chronic hepatitis occurs in 80% of patients.
- Cirrhosis occurs in 20% of chronic infection within 20 years.
- Once cirrhosis is present, **2 – 5% per year will develop hepatocellular carcinoma.**
- Risk factors for progression to cirrhosis are:
 - Male gender
 - Immunosuppression (e.g. HIV)
 - Heavy alcohol misuse

○ Extra-Hepatic Syndrome:

- Cryoglobulinemia
- Porphyria Cutanea Tarda
- Membranoproliferative glomerulonephritis
- Monoclonal gammopathy of unknown significance (MGUS)
- Non-Hodgkin lymphoma

■ Serology & Diagnosis:

- LFTs = episodic elevation in serum aminotransferases
- HCV-RNA = positive within 1–3wk, marker of active infection;
- Anti-HCV-IgG = is not protective antibody i.e. it doesn't mean recovery or immunity.
Measured by ELISA.
- HCV RIBA = it is confirmatory test, used to confirm a positive anti – HCV ELISA.
RIBA = recombinant immunoblot assay
- Diagnosis:
 - Acute infection = positive HCV RNA ± anti-HCV
 - Resolved infection = negative HCV RNA ± anti-HCV
 - Chronic infection = positive HCV RNA, positive anti-HCV

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Treatment:

- Goal of treatment is to eradicate the infection.
- Indications:
 - Acute Infection:
 - If no spontaneous clearance at 8 – 12 weeks.
 - Agents: Pegylated Interferon- α \pm Ribavirin x 12 – 24 weeks.
 - Chronic Infection:
 - **Positive HCV RNA, PLUS:**
 - **Biopsy showing chronic hepatitis & fibrosis (stage > 1) – OR:**
 - **Biopsy showing compensated liver disease**
 - In genotypes 2 & 3 treatment can be started without biopsy (due to high response rate).
- **Triple Therapy (Genotype-1):**
 - Pegylated Interferon- α (PEG-IFN α), PLUS:
 - Ribavirin, PLUS, Protease Inhibitor (Boceprevir, Telaprevir)
 - Treatment duration – 24 – 48 weeks.
- **Dual Therapy (Genotypes 2, 3):**
 - Pegylated Interferon- α (PEG-IFN α), PLUS, Ribavirin.
 - Treatment duration – 24 weeks.
- **Goal of Therapy:**
 - The goal of therapy is “**Sustained Virological Response (SVR)**”.
 - SVR is defined as loss of virus from serum (i.e. negative HCV-RNA) 6 months after completing therapy.
 - “**Early Virological Response (EVR)**” is defined as negative HCV-RNA within 1 month after starting therapy.
- **Hepatitis C Genotypes:**
 - Genotypes 2 & 3:
 - Good response to treatment.
 - Average treatment duration is 24 weeks.
 - SVR rate is about 70% after 6 months therapy.
 - Genotypes 1 & 4:
 - Average response to treatment.
 - Average treatment duration is 48 weeks.
 - SVR rate is about 40% after 12 months therapy.

Autoimmune Hepatitis:

I. Introduction:

- It is a liver disease of unknown etiology characterized by a strong association with other autoimmune diseases, high levels of serum immunoglobulins and antibodies in the serum.
- Types:
 - **Type-I Autoimmune Hepatitis:**
 - It is associated with HLA-DR3 and DR4.
 - It is associated with other autoimmune diseases such as pernicious anemia, thyroiditis, celiac disease, Coomb's positive hemolytic anemia.
 - It occurs most frequently in girls and young women.
 - Characterized by:
 - Antinuclear antibody (ANA) = positive
 - Anti-smooth muscle antibody (ASMA) = positive
 - **Type-II Autoimmune Hepatitis:**
 - It usually occurs in children (age 2 – 14 years).
 - Characterized by:
 - Anti-liver/kidney microsomal (anti-LKM) = positive
 - ANA = negative
 - ASMA = negative
 - **Type-III Autoimmune Hepatitis:**
 - Characterized by:
 - Serum immunoglobulins = elevated
 - Anti-soluble liver antigen (anti-SLA) = positive
 - ANA = negative
 - ASMA = negative

II.

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Management:

- Indications for Treatment:
 - If LFTs 10 times upper limit of normal – OR:
 - If LFTs 5 times upper limit of normal, PLUS:
 - IgG levels ≥ 2 times upper limit of normal – OR:
 - Liver biopsy showing bridging or multi-acinar necrosis.
- Acute Exacerbations:
 - Corticosteroids are the treatment of choice.
 - Prednisolone 40 mg/day PO, then gradually titrated as LFTs improve.
- Maintenance Therapy:
 - **Low-dose Prednisolone (5 – 10 mg/day) + Azathioprine (1 – 1.5 mg/kg/day)**
 - Azathioprine can also be used as monotherapy.
 - Approximately 50% of symptomatic patients will die of liver failure within 5 years.

Hepatic Failure, ALD, & NAFLD

Acute Hepatic Failure:

I. Introduction:

- It is defined as hepatic encephalopathy occurring as a result of sudden, severe impairment of liver functions in a patient with a previously normal liver.
- **Causes:**
 - Acute viral hepatitis = most common cause worldwide.
 - Paracetamol toxicity = most common cause in UK.
 - Drugs:
 - Acetaminophen (paracetamol); Isoniazid; Rifampin, Sulfonamides
 - Anti-depressants; Methyl dopa; tetracycline; Amiodarone; Propylthiouracil
 - Toxins:
 - Mushroom – amanita phalloides
 - Fluorinated hydrocarbons
 - Miscellaneous:
 - Idiopathic
 - Reye's syndrome
 - HELLP syndrome
 - Acute fatty liver of pregnancy

Classification of Acute Liver Failure

Type	Time: jaundice to encephalopathy	Cerebral Edema	Common Causes
Hyperacute	< 7 days	Common	Viral, paracetamol
Acute	8 – 28 days	Common	Cryptogenic, drugs
Sub-acute	29 days – 12 weeks	Uncommon	Cryptogenic, drugs

II. Clinical Features:

- **Neurologic:**
 - Hepatic encephalopathy – cardinal manifestation of acute liver failure
 - Asterixis
 - Cerebral edema:
 - Raised intracranial pressure causing:
 - Cerebral hypoxia, uncal herniation,
 - **"Cushing's reflex"** (hypertension + bradycardia)

▪ **Systemic Features:**

- CVS = Hypotension with low systemic vascular resistance
- Pulmonary = Respiratory alkalosis
- Renal = acute tubular necrosis, HRS, hyponatremia, hypokalemia
- Hematologic = coagulopathy with or without DIC
- Endocrine = hypoglycemia; metabolic acidosis, adrenal insufficiency
- Hepatobiliary:
 - Jaundice (in Reye's syndrome jaundice is rare)
 - Splenomegaly is uncommon.
 - Ascites and edema indicates advanced stage.
 - Liver:
 - Initially = normal; later = small in size
 - Hepatomegaly + sudden ascites = Budd-Chiari syndrome

III. Investigations:

- Toxicology screen of blood and urine
- Viral serologies (hepatitis B core IgM is the best screening test for acute HBV infection).
- Autoimmune hepatitis serologies
- Ceruloplasmin, serum and urinary copper.
- Ultrasound of liver and Doppler of hepatic veins.

IV.



Management:

- Admit in ICU for hemodynamic and ventilatory support.
- Intravenous N-acetylcysteine:
 - Indicated in all patients with hepatic failure & grade 1 – 2 encephalopathy
 - It increases cerebral blood flow and increases transplant-free survival.
- Cerebral edema:
 - Elevation of head of bed to 30°.
 - Hypertonic saline for goal Na of 145 – 155 mEq/L.
 - Intravenous mannitol (1g/kg bodyweight).
 - Hyperventilation
- Coagulopathy:
 - Intravenous vitamin K, platelets
 - Fresh frozen plasma (FFP)
- Electrolyte imbalance:
 - Dextrose for hypoglycemia.
 - Anticipate and correct hypokalemia, hypocalcemia, hypomagnesaemia, hypophosphatemia.
- Treatment of specific causes e.g.:
 - Nucleosides for hepatitis B; corticosteroids for autoimmune hepatitis.
 - Chelation therapy for Wilson's disease; IV acyclovir for herpes simplex
 - Gastric lavage and charcoal ± penicillin & silymarin for Amanita phalloides.
 - Liver transplantation is the treatment of choice.

Poor Prognostic Factor in Acute Liver Failure:**Non – Paracetamol Cases:**

- Prothrombin time > 100 seconds.
OR
- Any 3 of the following:
 1. Jaundice to encephalopathy time of > 7 days
 2. Age < 10 or > 40 years
 3. Drug – induced or Non-A – E hepatitis
 4. Bilirubin > 300 $\mu\text{mol/L}$ (=17.6 mg/dL)
 5. Prothrombin time > 60 seconds
- OR
- Factor V level < 15% and encephalopathy grade 3 or 4

Paracetamol Cases:

- Arterial pH < 7.3 (acidosis)
OR
- Serum creatinine > 300 $\mu\text{mol/L}$, plus
- Prothrombin time > 100 seconds, plus
- Grade III – IV encephalopathy

Alcoholic Liver Disease (ALD):**I. Introduction**

- It refers to hepatic changes in patients with chronic alcohol consumption.
- It presents in three forms:
 - Alcoholic steatosis (alcoholic fatty liver disease) – reversible
 - Alcoholic hepatitis – reversible
 - Alcoholic cirrhosis – irreversible
- Only 10% of alcoholics have evidence of cirrhosis at post-mortem.
- Alcoholic liver disease does not occur below a threshold of 21 units/week in women and 28 units/week in men.

II. Clinical Features:

- Alcoholic Steatosis:
 - Elevated transaminases in the absence of hepatomegaly.
 - It has good prognosis; steatosis disappears after 3 months of abstinence.
- Alcoholic Hepatitis:
 - Jaundice and hepatomegaly.
 - Portal hypertension and its complications; malnutrition.

- Alcoholic Cirrhosis:
 - Stigmata of chronic liver disease
 - Liver can be normal, large or small.
 - Ascites, varices, and encephalopathy
 - Hepatocellular carcinoma.

III. Diagnosis:

- CBC:
 - Macrocytosis (MCV > 100), without anemia.
 - Remember: alcohol causes macrocytic anemia, not megaloblastic anemia, therefore it doesn't cause hypersegmented neutrophils.
- LFTs:
 - **Raised transaminases (AST >> ALT)**
 - Raised gamma-glutamyltransferase (GGT)
 - Increased total bilirubin and INR indicate severe hepatitis.
- Discriminant Function (DF)
 - Also known as "Maddrey's Score";
 - Predicts prognosis by using prothrombin time (PT) and bilirubin.

$$DF = [4.6 \times \{\text{patient's PT} - \text{control PT}\} + \text{total bilirubin in mg/dL}]$$

IV.

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Treatment:

- Cessation of alcohol consumption is the most important treatment.
- Corticosteroids decrease mortality in:
 - Those with encephalopathy
 - Those with DF score of > 32.
- Pentoxifylline decreases mortality due to reduction in hepatorenal syndrome.
- Liver transplantation

Non-Alcoholic Fatty Liver Disease (NAFLD):

I. Introduction:

- **Definition:**
 - NAFLD is defined as fatty infiltration of the liver, AND:
 - Absence of alcohol or other cause of liver steatosis.
 - NASH is non-alcoholic steatohepatitis.
 - NASH is defined as NAFL + inflammation ± fibrosis on liver biopsy.
- **Risk Factors** (metabolic syndrome):
 - Obesity
 - Dyslipidemia

- Hyper-insulinemia
- Insulin resistance
- Type-2 diabetes mellitus

▪ **Epidemiology:**

- No sex predilection (male = females)
- It accounts for 70% cases of chronic hepatitis of unknown cause.
- It eventually causes cirrhosis in 10 – 30% of cases.
- It is the most common cause of “cryptogenic cirrhosis”.
- Increased risk of hepatocellular carcinoma.

II. Clinical Features & Management:

▪ **Clinical Features:**

- Asymptomatic
- Always suspect in patient with metabolic syndrome who present with asymptomatic abnormal LFTs.
- Elevation of transaminases (ALT >> AST), OR
- Isolated elevation of gamma-glutamyltransferase (GGT).
- It rarely can present with complications of cirrhosis (e.g. Variceal bleeding)

Clinical Pearl:

NAFLD v/s NASH:

- It is important to differentiate NAFLD, which doesn't require follow-up, from NASH.
- Features that suggest NASH are as follows:
 1. Elevated aminotransferases (> 2x normal)
 2. Metabolic syndrome
 3. Liver biopsy (only definitive way to distinguish):
 - Macrovesicular steatosis; Mallory bodies
 - Neutrophil infiltration, and pericellular fibrosis

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Treatment:

- Weight loss and exercise to reduce BMI and insulin resistance
- Type-II DM + NAFLD = metformin is the drug of choice.
- Lipid Control – use statins
- **Pioglitazone + high-dose Vitamin E decrease steatosis & inflammation, but not fibrosis**
- This combination is associated with increased risk of prostate cancer.
- Liver transplantation

Inherited Liver Diseases

I. Hemochromatosis:

- It is characterized by the excessive accumulation of body iron, leading to tissue injury.
- **Types:**
 - Hereditary Hemochromatosis:
 - Autosomal recessive disorder (HFE gene on chromosome 6)
 - Male dominant; mostly after 40 years.
 - Most common HFE gene mutation is C282Y mutation.
 - Mechanism: increased small intestine absorption of iron
 - Secondary Hemochromatosis:
 - Blood transfusions (long-term dialysis, sickle cell anemia)
 - Ineffective erythropoiesis (beta thalassemia, sideroblastic anemia)
 - Increased oral intake of iron
 - Chronic liver disease
- **Clinical Features:**
 - Symptomatic disease presents in men ≥ 40 years of age with following features:
 - Liver = micronodular cirrhosis and **hepatocellular carcinoma**
 - Pancreas = **diabetes mellitus (bronze diabetes)**
 - Skin = **hyperpigmentation (due to excess melanin)**
 - Heart = restrictive cardiomyopathy, CHF
 - Gonads = hypogonadism (testicular atrophy, impotence, loss of libido)
 - Bones & joints = arthropathy of metacarpophalangeal joints.
- **Diagnosis:**
 - Increased serum iron and serum ferritin,
 - Decreased total iron binding capacity (TIBC).
 - **Transferrin saturation (i.e. serum iron \div TIBC) of $> 45\%$ is highly suggestive of iron overload.**
 - ECG and echocardiography to rule out cardiomyopathy
 - HFE gene mutation screening.
 - **Liver biopsy to confirm the diagnosis**

R_x**Treatment:**

- Phlebotomy:
 - It is done weekly to rid the body of excess iron.
 - It involves weekly venesection of 500 ml blood (250 mg iron).
 - **Target is to reduce serum ferritin < 50 µg/L.**
 - It improves liver & cardiac problems.
 - It has less predictable role on joint pain – can even worsen it.
 - DM doesn't resolve with venesection.
 - Asymptomatic disease should also be TREATED to keep ferritin normal.
- Iron chelation therapy (deferroxamine) – if phlebotomy not tolerated.
- Screening for hepatocellular carcinoma – main cause of death
- Screening Indications:
 - Genetic screening of first-degree relatives
 - Liver biopsy is indicated:
 - Asymptomatic relatives with:
 - Abnormal LFTs, AND (OR):
 - Serum ferritin > 1000 µg/L

II. Wilson's Disease:

- Also known as “**hepatolenticular degeneration**”.
- It is genetic disorder of copper metabolism resulting in accumulation of toxic levels of copper.
- **Pathogenesis:**
 - Autosomal recessive disease
 - Characterized by decreased synthesis of ceruloplasmin (copper binding protein)
 - Mutations of WD gene on chromosome 13,
 - Normal Condition:
 - Copper is absorbed in the proximal small intestine.
 - It is rapidly taken into the liver, where it is stored and incorporated into ceruloplasmin.
 - Wilson's Disease:
 - Intestinal copper absorption and transport into the liver are intact.
 - Copper incorporation into ceruloplasmin in hepatocytes and its excretion into bile are impaired.
 - Copper, therefore, accumulates in liver and later in other organs.
 - Defective hepatocyte transport of copper into bile for excretion

▪ Clinical Features:

- Symptoms usually appear between the ages of 5 – 45 years.
- Liver:
 - Acute hepatitis; or fulminant hepatic failure
 - Chronic hepatitis; or micronodular cirrhosis.
- Eye (**Kayser-Fleischer rings**):
 - These are greenish-brown discoloration of cornea, appear first at upper margin.
 - It is seen in 60% cases with hepatic disease & 99% cases with neurologic disease.
 - These rings are due to copper deposits in Descemet's membrane.
 - These rings are visible on slit-lamp examination.
 - These rings are the most important single clinical clue to diagnosis.
 - They eventually disappear with treatment.
- CNS:
 - Movement disorders = copper deposits in putamen (tremors)
 - Hemi-ballismus = copper deposits in sub-thalamic area
 - Dementia = copper is toxic to cerebral cortex neurons
 - Parkinsonism
- Affective Features:
 - Depression; Mania
 - Personality changes
 - Delusions
 - Quick to anger, slow to solve problems.

▪ Diagnosis:

- Decreased serum ceruloplasmin – **best single clue to the diagnosis.**
- Increased urinary excretion of copper.
- Serum copper levels may be low, high, or normal and is therefore of no diagnostic value.
- **Liver biopsy = increased hepatic copper content**
- **Confirmatory Test:**
 - 24-hour urinary Cu excretion while giving Penicillamine.
 - Urinary Cu > 24μmol/day is diagnostic.

R_x**Management:**

- Avoid foods with high copper content (liver, chocolates, nuts, legumes)
- **Penicillamine:**
 - It is a copper-binding agent – drug of choice.
 - It is given for life, continued even through pregnancy.
 - Abrupt discontinuation must be avoided – risk of acute liver failure.
 - Side-Effects:
 - Rash
 - Protein-losing Nephropathy
 - Lupus-like syndrome
 - Bone marrow depression
- Alternative Agents:
 - Trientine dihydrochloride – 1.2 – 2.4 g/day.
 - Zinc (50 mg 3 times daily) – it inhibits copper reabsorption in intestine.
- Liver transplantation:
 - Fulminant liver failure
 - Advanced cirrhosis with liver failure.

III. α 1-Antitrypsin (AAT) Deficiency:

- AAT deficiency is autosomal recessive disorder marked by low levels of α 1-antitrypsin, a protease inhibitor.
- AAT deficiency is the most commonly diagnosed genetic liver disease in infants and children.
- AAT accumulates in hepatocytes and causes liver damage.
- **α 1-antitrypsin:**
 - α 1-antitrypsin is a protease inhibitor.
 - α 1-antitrypsin inhibits proteases, which are normally released from neutrophils during acute inflammation.
 - α 1-antitrypsin is produced by Pi gene on chromosome 14.
- **Pathogenesis:**
 - Normal genotype is PiMM (Pi stands for protease inhibitor)
 - Most common abnormal allele is Z
 - PiZZ variant:
 - These are homozygotes with **extremely** low levels of AAT in serum.
 - These individuals are at high risk for developing clinical disease.

- PiMZ variant:
 - These are heterozygotes with **moderately** low levels of AAT in serum.
 - These individuals are at medium risk for developing clinical disease.

▪ Clinical Features:

- Neonatal hepatitis with intrahepatic cholestasis
- Micronodular cirrhosis
- Risk for hepatocellular carcinoma
- Pan-acinar emphysema.

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Management:

- Quit cigarette smoking
- Supportive treatment of emphysema and liver complications
- Pooled AAT given intravenously (if FEV < 80% of predicted)
- Liver transplantation is treatment of choice in decompensated cirrhosis.

III. α₁-Antitrypsin (AAT) Deficiency:

- AAT deficiency is autosomal recessive disorder marked by low levels of α₁-antitrypsin, a protease inhibitor.
- AAT deficiency is the most commonly diagnosed genetic liver disease in infants and children.
- AAT accumulates in hepatocytes and causes liver damage.
- Pathogenesis:
 - α₁-antitrypsin is a protease inhibitor.
 - α₁-antitrypsin inhibits proteases, which are normally released from neutrophils during acute inflammation.
 - α₁-antitrypsin is produced by P₁ gene on chromosome 14.
- Pathogenesis:
 - Normal genotype is P₁MM (P₁ stands for protease inhibitor).
 - Most common abnormal allele is Z.
 - P₁ZZ variant:
 - These are homozygotes with extremely low levels of AAT in serum.
 - These individuals are at high risk for developing clinical disease.

Intrahepatic Biliary Tract Diseases

I. Primary Biliary Cirrhosis (PBC):

- It is a chronic, progressive cholestatic liver disease of unknown cause, possibly autoimmune.
- It is characterized by destruction of “Intra-Hepatic Bile Ducts”.
- **Clinical Features:**
 - Most commonly presents in middle-aged women (female : male is 6 : 1)
 - **Pruritus – most common initial complaint.**
 - Jaundice
 - Osteomalacia – due to fat-soluble vitamin deficiency (A, D, E, K)
 - Osteoporosis – hepatic osteodystrophy
 - Skin xanthomas (focal accumulations of cholesterol).
 - Hepatomegaly is constant feature.
 - Splenomegaly (late feature when portal HTN occurs)
 - Most common cause of death = liver failure
- **Associations:**
 - Sjogren’s syndrome
 - Raynaud’s phenomenon
 - Celiac disease
 - Systemic sclerosis
- **Diagnosis:**
 - Elevated serum cholesterol.
 - **Cholestatic Jaundice** i.e.:
 - Conjugated hyperbilirubinemia
 - Elevated alkaline phosphatase (ALP)
 - Elevated gamma glutamyltransferase (GGT).
 - Increased serum IgM.
 - **Anti-mitochondrial antibody (AMA):**
 - It is positive in > 95% cases.
 - **It is highly sensitive & specific – if positive, NO NEED for biopsy.**
 - **Liver Biopsy:**
 - Lymphocytic infiltrate in portal tracts.
 - Granulomatous destruction of bile ducts.

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Treatment:

- Ursodeoxycholic acid – it slows progression of disease (mainstay of treatment).
- Pruritus:
 - First-line agent = “Cholestyramine” – it is anion-binding resin
 - Second-line agents (if patients do not respond to cholestyramine):
 - Rifampicin – (max. dose up to 600 mg/day)
 - Naltrexone (opioid antagonist)
 - Plasmapheresis & liver support device
- Fat-soluble vitamin supplementation.
- Calcium and vitamin D for osteoporosis.
- **Liver transplantation (definitive treatment)** – once liver failure has developed.

II. Secondary Biliary Cirrhosis:

- It is due to prolonged extra-hepatic biliary obstruction, which results in intra-hepatic injury.
- Prolonged extra-hepatic biliary tract obstruction results from:
 - Gall stones (most common)
 - Biliary atresia
 - Bile duct strictures
 - Carcinoma of head of pancreas.
- It has similar clinical presentation as PBC.
- It is differentiated from PBC by:
 - No sex predilection.
 - Serum IgM – negative
 - Serum AMA – negative.

III. Primary Sclerosing Cholangitis (PSC):

- It is a chronic, progressive cholestatic liver disease of unknown cause, possibly autoimmune.
- It is characterized by progressive inflammation, fibrosis, and strictures of “**Extra-Hepatic & Intra-Hepatic Bile Ducts**”.
- **Clinical Features:**
 - Most commonly presents in young males 20 – 50 years (female: male is 1: 2).
 - Progressive jaundice, pruritus and fatigue.
 - **Increased risk for cholangiocarcinoma.**
 - Associations:

- **Ulcerative colitis – most common**
- Crohn's disease (much rare)
- Retro-peritoneal fibrosis.
- Chronic pancreatitis
- HIV infection

▪ **Diagnosis:**

- Cholestatic Jaundice i.e.:
 - Conjugated hyperbilirubinemia
 - Elevated alkaline phosphatase (ALP)
 - Elevated gamma glutamyltransferase (GGT).
- MRCP/ERCP:
 - **"Beading" appearance** i.e.
 - Multiple areas of bile duct strictures and dilatations.
- Liver Biopsy:
 - Periductalportal tract "onion-skin" fibrosis and inflammation.
 - Segmental stenosis of extrahepatic & intrahepatic bile ducts

R_x

Management:

- Ursodeoxycholic acid – improves cholestasis
- Cholestyramine – for pruritus
- Antibiotics for bacterial cholangitis
- Fat-soluble vitamin replacement.
- Yearly ultrasound to detect cholangiocarcinoma
- Immunosuppressants (e.g. azathioprine) – disappointing results.
- **Liver transplantation – definitive treatment.**

Hepatic Vascular Disorders

I. Budd-Chiari Syndrome:

- It refers to thrombosis of larger hepatic veins and sometimes inferior vena cava causing hepatic vein outflow obstruction.
- **Causes:**
 - Idiopathic – 10% cases.
 - Primary polycythemia vera
 - Oral contraceptives
 - Pregnancy
 - Paroxysmal nocturnal hemoglobinuria
 - Inherited disorders of coagulation (anti-thrombin III, protein C, or protein S deficiencies)
- **Clinical Manifestations:**
 - **Painful hepatomegaly – is almost always present.**
 - Acute Presentation:
 - Sudden onset upper abdominal pain.
 - Marked ascites and occasionally liver failure.
- **Diagnosis:**
 - LFTs = increased transaminases.
 - Ascitic fluid analysis = exudative ascites
 - MRI – OR – Venography:
 - Occlusion of hepatic veins and IVC.
 - **Increased size of caudate lobe (due to separate venous drainage)**
- **Treatment:**
 - Acute onset (suspected thrombosis) = thrombolysis with streptokinase.
 - Anticoagulation with heparin followed by warfarin.
 - Hepatic venous strictures:
 - If short = angioplasty
 - If extensive = TIPSS – preferred (surgical shunts less commonly performed)
 - Liver Transplantation(Indications):
 - Progressive liver failure – along with life-long anti-coagulation
 - Failed shunt
 - Fulminant presentation.

II. Veno-Occlusive Disease:

- Also known as "Sinusoidal Obstruction Syndrome".
- It is a condition characterized by occlusion of hepatic venules and sinusoids – **"Small Central Hepatic Veins"**.
- It is caused by obliteration & fibrosis of terminal hepatic venules due to deposition of red cells, hemosiderin-laden macrophages, & coagulation factors.
- **Causes:**
 - Hematopoietic stem cell transplantation (HSCT) – usually within first 20 days
 - Chemotherapy (especially cyclophosphamide)
 - Radiotherapy
 - Jamaican bush tea
- **Clinical Features:**
 - Tender hepatomegaly
 - Ascites, Weight gain, Jaundice
 - Radiologically the large hepatic veins are patent – unlike Budd-Chiari syndrome.
- **Management:**
 - Spontaneous recovery in 70 – 85% cases.
 - Death in remaining cases.
 - Treatment is supportive.
 - **Defibrotide:**
 - It is adenosine agonist that increases the levels of tissue plasminogen activator.
 - It binds to vascular endothelial cells & promote fibrinolysis.

III. Portal Vein Thrombosis (PVT):

- Definition: It refers to thrombosis, constriction, or invasion of portal vein leading to portal HTN, and its complications (varices).
- **Causes:**
 - Cirrhosis
 - Neoplasm – Pancreatic, Hepatocellular
 - Abdominal infection – pylephlebitis (infection of portal vein)
 - Hypercoagulable state
 - Pancreatitis
 - Inflammatory bowel disease
 - Surgery, Trauma

▪ Clinical Features:

- Acute PVT:
 - Abdominal Pain
 - Intestinal infarction – if involves mesenteric vein
 - Fever – suspect pylephlebitis
- Chronic PVT:
 - Asymptomatic
 - Portal HTN – (ascites, varices, splenomegaly, hepatic encephalopathy)

▪ Management:

- Evaluate for underlying cause.
- Treatment is less clear for cirrhotic patients.
- Acute PVT – Heparin followed by warfarin x 6 months (for life if irreversible cause)
- Chronic PVT – anticoagulate if non-cirrhotic & those with hypercoagulable state.
- Prophylaxis – LMWH may prevent PVT & liver decompensation in advanced cirrhosis

III. Portal Vein Thrombosis (PVT):

Definition: It refers to thrombosis, constriction, or invasion of portal vein leading to portal HTN and its complications (varices).

Causes:

- Cirrhosis
- Neoplasm – Pancreatic, Hepatocellular
- Abdominal infection – pylephlebitis (infection of portal vein)
- Hypercoagulable state
- Pancreatitis
- Inflammatory bowel disease
- Surgery, Trauma

Liver Tumors

Benign Tumors:

I. Cavernous Hemangioma:

- It is the most common benign tumor of liver.
- It is a rare cause of intraperitoneal hemorrhage.

II. Live Cell Adenoma:

- It is benign tumor of hepatocytes.
- It is more common in women and associated with oral contraceptives.

Malignant Tumors:

I. Hepatocellular Carcinoma:

- It is the most common primary malignant tumor of the liver.
- Age = 5th to 6th decade.
- Male > female.
- Causes:
 - Chronic HBV and HCV
 - Cirrhosis
 - Aflatoxin (due to *Aspergillus flavus*)
 - Hereditary hemochromatosis
 - α 1-antitrypsin deficiency
 - Wilson's disease



Morphology:

- - Focal, multifocal, or diffusely infiltrative
 - Neoplastic cells are arranged in nests, with central lumen
 - **Neoplastic cells characteristically contain bile.**
 - Invasion of vascular channels (portal and hepatic veins)
- Clinical Findings:
 - Mostly asymptomatic and discovered on screening.
 - Hepatomegaly (right upper quadrant mass)
 - Ascites jaundice, worsening LFTs, and variceal hemorrhage.
 - Weight loss, anorexia, and abdominal pain
- Metastasis& Paraneoplastic Features:
 - Primarily via venous invasion into hepatic vein system.
 - Hematogenous spread occurs to **LUNG** first, then to other sites.

- Production of ectopic hormones:
 - Erythropoietin (secondary polycythemia)
 - Insulin-like factor (hypoglycemia)
- **Investigations:**
 - **Increased serum α -fetoprotein (AFP)** – 60% cases.
 - Sudden increase in serum ALP and GGT.
 - Ultrasound and CT scan to localize the tumor.
 - Liver biopsy
- **Management:**
 - Non-cirrhotic patients = Hepatic resection is best.
 - Cirrhotic patients = Liver transplantation is best.
 - Tumors ≤ 3 cm = percutaneous ablation with ethanol injection into the tumor.
 - Cirrhotic patients with unresectable tumor = hepatic artery embolization with Gelfoam and Adriamycin.

III. Metastatic Tumor:

- It is the most common liver cancer.
- It is caused by following primary sites:
 - Lung – most common
 - Breast; Colon; Leukemia; Lymphoma

Gallbladder Diseases

Cholelithiasis (Gallstones):

I. Introduction:

- It is the most common disorder of the biliary tree.
- Bile contains bile salts, phospholipids, and cholesterol.
- Gallstone formation is promoted by: increased cholesterol saturation in bile + accelerated nucleation + gallbladder hypomotility.
- **Risk Factors:** (mnemonic 4Fs)
 - Female
 - Forty (increases after 40 years)
 - Fatty (obesity)
 - Fertile (pregnancy)
 - Rapid weight reduction
 - Drugs (oral contraceptive pills, estrogen, Octreotide)
- **Types of Gallstones:**
 - Cholesterol Stones (90%):
 - These stones are more common in West than Asia.
 - These stone have two subtypes:
 - Mixed stone = > 50% cholesterol, smaller and multiple
 - Pure stone = 100% cholesterol, larger, yellow, white appearance.
 - Pigment Stones.
 - These stones are seen in Asians more than the Western.
 - These stones have two subtypes:
 - (i). Black Stones:
 - These stones contain unconjugated bilirubin and calcium.
 - These are seen in chronic hemolysis and cirrhosis.
 - (ii). Pigment Stones:
 - These stones contain calcium bilirubinate and crystals with calcium palmitate.
 - These stones arise due to bile stasis and infection in bile ducts, such as:
 - Duodenal diverticula
 - Biliary strictures
 - Parasitic infections

▪ Clinical Features:

- Asymptomatic in 70 -80% of cases.
- Asymptomatic patients convert to symptomatic ones at rate of 1 – 3% per year.
- Biliary Colic:
 - Sudden onset post-prandial abdominal pain.
 - Pain is located in right upper quadrant pain.
 - Nausea and vomiting, dyspepsia, and flatulence.
 - No fever.

II. Management:

▪ Treatment:

- Cholecystectomy, if symptomatic.
- Ursodeoxycholic acid, if poor surgical candidate (rare)

▪ Complications:

- Cholecystitis (most common)
- Common bile duct obstruction
- Gallbladder cancer
- Gallstone ileus
- Acute pancreatitis

Acute Cholecystitis:

I. Introduction:

- It refers to acute inflammation of the gallbladder.

▪ Types:

(a). Acute Calculous Cholecystitis:

- It is characterized by obstruction of neck and cystic duct.
- It is caused by gallstones.

(b). Acute Acalculous Cholecystitis:

- It results from causes not associated with stones.
- Causes:
 - Severe trauma; Severe burns
 - Multisystem organ failure
 - Postpartum state; Postoperative state.

▪ Clinical Findings:

- Fever, nausea, vomiting, after 15 – 30 minutes after eating
- Pain is epigastric initially.
- Pain then shifts to right upper quadrant, referred to right scapula.
- **Murphy's sign** i.e. RUQ tenderness during inspiration by the examiner's right subcostal palpation.
- **Courvoisier's sign** i.e. palpable non-tender gallbladder.

II. Management:▪ **Lab Findings:**

- Leukocytosis
- Elevated serum alkaline phosphatase
- Hyperbilirubinemia (suggests common bile duct obstruction)
- **Ultrasound is gold standard investigation:**
 - Gallbladder wall thickening > 5 mm.
 - Pericholecystic fluid
- HIDA scan (hepatobiliary iminodiacetic acid) = if US doesn't show diagnosis.

▪ **Treatment:**

- Nothing per oral (NPO).
- Intravenous fluids and analgesia
- Antibiotics
- Cholecystectomy:
 - Early i.e. within 5 days of onset of symptoms after symptoms have resolved.
 - Urgent cholecystectomy is indicated when:
 - Symptoms fail to resolve with medical therapy.
 - Increasing pain and fever
 - Empyema or gangrene of gallbladder

Carcinomas:**I. Carcinoma of the Gallbladder:**

- Sex = female dominant
- Age = 70 years
- **Morphology:**
 - Most common type = adenocarcinoma
 - Most common site = fundus and the neck
 - Liver invasion = occurs early and centrifugally
 - Growth patterns:
 - Infiltrating (common)
 - Exophytic
- Seeding Sites:
 - Peritoneum
 - GIT; Lungs

II. Cholangiocarcinoma:

- It is the most common malignancy of biliary tree.
- It arises from bile ducts within and outside of the liver.
- **Risk Factors:**
 - Primary Sclerosing cholangitis
 - Choledochal cyst and Caroli disease
 - Opisthorchis sinensis (Liver Fluke)
 - Thorotrast exposure (thorium dioxide)
- **Site:**
 - Ampulla of Vater & common bile duct (most common sites)
 - Junction of right/left hepatic duct (**Klatskin tumor**)
 - Intrahepatic bile ducts
- **Clinical Features:**
 - Obstructive jaundice (elevated bilirubin with markedly elevated ALP)
 - Palpable non-tender gall bladder (**Courvoisier's sign**)
 - Hepatomegaly
 - Weight loss, anorexia
 - Poor prognosis

Chapter 11

HEMATOLOGY



Red Blood Cell (RBC) Disorders

I. RBC Indices:

Measurement	Normal Range
Hemoglobin (Hb)	Men: 13.6 – 17.2 gm/dL Women: 12.0 – 15.0 gm/dL
Red cell count ($10^6/\mu\text{L}$)	Men: 4.3 – 5.9 Women: 3.5 – 5.0
Mean Corpuscular (Cell) Volume (MCV): ▪ It is the average volume of red blood cell.	82 – 96 cubic micrometers (femtoliters)
Mean Corpuscular Hemoglobin (MCH) ▪ It refers to average mass of Hb per RBC.	27 – 33 pg (picograms)
Mean Corpuscular Hemoglobin Concentration (MCHC) ▪ It is the average Hb concentration in RBCs	33 – 37 gm/dL
Red Cell Distribution Width (RDW) ▪ Reflects variation in size of RBCs in the peripheral blood.	11.5 – 14.5

II. The Peripheral Blood Film

	<u>Term</u>	<u>Meaning/ Association</u>
1	Anisocytosis	Abnormal size (e.g. megaloblastic anemia, thalassemia)
2	Poikilocytosis	Abnormal shape (e.g. myelofibrosis, thalassemia)
3	Acanthocytes	Spicules on RBCs (due to unstable RBC membrane lipid structure) Causes: splenectomy, abeta-lipoproteinemia, spherocytosis.
4	Burr Cells (echinocytes)	Spicules on RBCs but less marked than Acanthocytes. Causes: renal failure (uremia), liver failure.
5	Schistocytes	Fragmented RBCs sliced by fibrin bands Causes: microangiopathic hemolytic anemias, DIC, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pre-eclampsia.
6	Dimorphic Picture	Two populations of RBCs. Causes: sideroblastic anemia, after treatment of iron, Vit.B12, and folate deficiency anemia.
7	Rouleaux Formation	RBCs stack on each other. Seen in multiple myeloma, para-proteinemia and chronic inflammation
8	Basophilic stippling	Denatured RNA found in RBCs. Seen in lead poisoning, reticulocytosis, liver disease and megaloblastic anemia,
9	Bite cells & Heinz bodies	Seen in Glucose-6-phosphate dehydrogenase deficiency.
10	Reticulocytes:	<ul style="list-style-type: none"> ▪ Reticulocytes are larger spherical red cells with bluish color due to free ribosomal RNA. ▪ Reticulocytes don't have any nucleus and takes about 1 day to form mature RBCs. ▪ Reticulocyte count refers to percentage (%) of red cells in peripheral blood. ▪ Reticulocyte count is the marker of effective erythropoiesis (i.e. bone marrow response to anemia).

Hematocrit =

III. Anemia:

- Definition: decrease in RBC mass:
 - Men = hematocrit (Hct) < 41% - OR - hemoglobin (Hb) < 13.5 g/dL
 - Women = Hct < 36% - OR - Hb < 12 g/dL
- **Anemia is classified on the basis of mean corpuscular volume (MCV).**
- Classification of anemia requires the knowledge of reticulocyte-index.
 - **Reticulocyte index (RI)** refers to corrected reticulocyte count.
 - RI is calculated by following formula: *#% of red cell in peripheral blood.*
 - $$RI = \frac{\text{reticulocyte count} \times \text{patient's hematocrit (Hct)}}{\text{normal hematocrit}}$$
 - Normal hematocrit is 45%.
 - RI > 2% means adequate bone marrow response.
 - RI < 2% means hypo-proliferation (inadequate response)

Microcytic Anemia (MCV < 80 μm^3)

- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease
- Sideroblastic anemia

normal for rbc is low.

Macrocytic Anemia (MCV > 100 μm^3)

- Megaloblastic anemia
(Vit. B12 & Folate deficiency) *→ except.*
- Alcoholic liver disease
- Hypothyroidism
- Myelodysplastic syndromes

Normocytic Anemia (MCV 80 - 100 μm^3)

Low Reticulocyte Count (<2%)

- Blood loss < 1 week.
- Aplastic anemia?
- Renal failure
- Early-stage iron deficiency anemia
- Early-stage anemia of chronic disease.

High Reticulocyte Count (>2%)

- Intrinsic RBC defect:
 - Sickle cell anemia
 - G6PD deficiency
 - Hereditary spherocytosis
 - Paroxysmal nocturnal hemoglobinuria
- Extrinsic RBC defect:
 - Blood loss > 1 week
 - Immune hemolytic anemia
 - Microangiopathic hemolytic anemia
 - Malaria

Microcytic Anemia

I. Iron Deficiency Anemia:

- Parade of medicine - deals with incidence, distribution, possible control of disease*
- **Epidemiology:**
 - It is the most common anemia. ①
 - It is the most common nutritional disorder in the world. ②
 - Dietary iron is reabsorbed in the duodenum.
 - Oxidized iron (Fe^{+3}) must be reduced (Fe^{+2}) for reabsorption in duodenum. *ferric → ferrous*
 - Iron from plants is in a non-heme, oxidized form (Fe^{+3}).
 - Iron from meat is in heme, reduced form (Fe^{+2}).
 - 80% of functional iron is found in hemoglobin; the rest is stored in marrow macrophages, myoglobin, and enzymes.
 - Ascorbic acid (vitamin C) reduces oxidized iron and is therefore important in iron reabsorption.

Causes:

- Dietary Lack - children, elderly
- Increased Utilization - pregnancy, lactation, children
- Impaired absorption:
 - Celiac disease - absence of villous surface in the duodenum.
 - Gastrectomy - absence of gastric acid, which helps in iron reabsorption.

① Blood Loss: - *men 4 PM, women*

- Gastrointestinal blood loss:
 - It is most common cause in men and post-menopausal women.
 - World-wide, hookworm and Schistosomiasis are the most common causes of gut blood loss.
 - It may also occur as result of peptic ulcer disease, gastritis, colorectal malignancy.
- Menorrhagia (most common cause in women < 50 years)
- Colorectal cancer (most common cause in patients > 50 years)

Clinical Features:

- Koilonychia (nail spooning) *ab. thin nails, loss of convexity, becoming flat or even in shape*
- Angular cheilosis *inflammation of 1 or both corners of mouth - red corners with skin breakdown & itching*
- Atrophic glossitis *soreness of tongue, inflammation with depapillation*
- Pica (consumption of non-nutritive substances such as ice, clay)

○ **Plummer-Vinson syndrome:**

- Iron deficiency anemia
- Esophageal web – dysphagia for solids only (not liquids)
- Atrophic glossitis
- Increased risk for squamous cell carcinoma of esophagus.

▪ **Lab Findings:**

○ Complete Blood Count (CBC)

- Microcytic anemia (MCV < 80)
- Thrombocytosis (increased platelet count) – why

○ Iron Profile:

- Decreased serum iron
- Increased total iron binding capacity (TIBC) – TIBC is increased only in this anemia.

▪ **Decreased ferritin – best single test to confirm iron deficiency**

- Decreased transferrin saturation < 15% ($\text{Fe/TIBC} \times 100$)
- Soluble transferrin receptor is increased.

* TIBC
* ferritin
* Transferrin saturation
* receptor

R_x

Treatment:

○ Ferrous sulphate 200 mg 8-hourly:

- It is given for 3 – 6 months.
- It provides 195 mg of elemental iron per day.

○ Ferrous gluconate 300 mg 12-hourly

- It is given when the patient is intolerant to ferrous sulphate, e.g. dyspepsia.
- It provides 70 mg of elemental iron per day.

○ Response to therapy:

- Hemoglobin should rise by 1g/dL every 7 – 10 days.
- Increased reticulocyte count within 7 days.

Normal Iron intake / day =
x net count a good blood

① Genetics
 ② heredit. Def. - ck
 ③

II. Thalassemia:

(i). Beta Thalassemia:

■ Introduction:

- It is an autosomal recessive disorder.
- It is characterized by decreased synthesis of β -globin chain with relative excess of α -chains.
- It is common in blacks, Greeks, and Italians.
- β -globin chains are two in number, and expressed post-natally only, therefore anemia manifests 6 – 9 months after birth.
- β -thalassemia is classified into two categories:
 - β^0 Thalassemia = total absence of β -globin chain
 - β^+ Thalassemia = reduced β -globin chain synthesis

■ Mutations:

- Point mutations are the most common.
- Splicing mutations are the most common type of point mutations.
- Splicing mutations most commonly involve the introns.
- Unlike α -thalassemia, gene deletions are not common.

■ Types:

Beta-thalassemia Minor

- Genotype = β^0/β or β^+/β (heterozygotes with one mutated and one normal β -chain)
- It causes mild microcytic anemia *MCV < 80 fL*.
- It is mildly protective against falciparum malaria. *why*
- No transfusion is required.
- It is characterized by:
 - Microcytic anemia (MCV is more markedly low than in iron deficiency)
 - Iron profile is normal.
 - Hb electrophoresis:
 - Decreased HbA (adult hemoglobin 2 α 2 β)
 - Increased HbA₂ (2 α 2 δ)
 - Normal HbF (fetal hemoglobin 2 α 2 γ)

Beta-thalassemia Major:

- Also known as "Cooley's anemia".
- Genotype: 2 mutated β -chains:
 - Homozygous β^0 -thalassemia (β^0/β^0)
 - Homozygous β^+ -thalassemia (β^+/β^+)

- Features:
 - Severe microcytic anemia
 - Ineffective erythropoiesis (RBCs undergo apoptosis in marrow) ?
 - Requires blood transfusion. ?
 - Extra-medullary hematopoiesis (RBCs are made outside the marrow). ?
 - Extra-medullary hematopoiesis results in skull bossing (crew-cut appearance on X-ray), and hepatosplenomegaly. ?
 - Hemosiderosis and secondary hemochromatosis due to iron overload from multiple blood transfusions. ?
- Lab Findings:
 - Anisocytosis (variation in RBC size)
 - Poikilocytosis (variation in RBC shape)
 - Target cells (Hb collects in center of cells)
 - Reticulocyte count is increased.
 - Hb electrophoresis:
 - HbA = absent ?
 - HbA₂ = normal, high, or low ?
 - HbF = markedly increased ?

R_x**Treatment:**

- Folate supplementation (5mg daily)
- Transfusions to maintain hemoglobin > 10g/dL.
- Oral iron chelators for iron overload such as Deferoxamine and Deferasirox.
- Splenectomy: — why, ↓
 - When splenomegaly causes mechanical problems.
 - When there is ≥ 50% increase in transfusion needs. — why splenectomy Hb ↑
- Allogeneic bone marrow transplantation

(ii). Alpha Thalassemia:

- It is an autosomal recessive disorder.
- It is common in Southeast Asians, less so in Africans.
- It is characterized by decreased synthesis of α-globin chains with relative excess of β-chains.
- α-globin chains are four in number, and expressed both prenatally as well as post-natally.
- α-thalassemia is due to gene “deletions”, not due to point mutations.
- Types:

Normal - $\alpha/\alpha \alpha/\alpha$

(1). Silent Carrier:

pt 'does not' have any disease. symptom mild anemia.

- It is caused by deletion of one α -chain i.e. $-\alpha \alpha/\alpha$
- It is asymptomatic. - no p. sym.
- No red cell deformity.

1 α chain
 α symp.

gene deletion

(2). Alpha-thalassemia trait:

- It is caused by deletion of two α -chains i.e.
 - Asian type = $-\alpha/\alpha$ \rightarrow homo
 - African type = $-\alpha -/\alpha$ \rightarrow hetero
- It is asymptomatic like β -thalassemia minor.
- It is associated with mild microcytic anemia.

Q) What does Asym means?

A)

2 α chains
 α symp

(3). HbH Disease:

- It is caused by deletion of three α -chains i.e. $-\alpha -/\alpha$
- It is characterized by precipitation of β -chain tetramers.
- Features:
 - Chronic hemolysis \rightarrow patho
 - Jaundice, gallstone, and skeletal changes. \rightarrow patho
 - Increased reticulocyte count and intra-erythrocytic inclusions. \rightarrow ? patho
 - It produces severe anemia, but doesn't require regular transfusions.

3 α chains

(4). Hydrops Fetalis:

- It is caused by deletion of all four α -chains. \rightarrow 4 α chain
- It is the most severe form, and is incompatible with life.
- It is characterized by precipitation of γ -chain (gamma-chain) tetramers (hemoglobin Barts).
- Survival in early development is due to expression of Gower Hb i.e. $\xi_2\gamma_2$.
- Signs of fetal distress become evident by the 3rd trimester.

does however req. transfusions

III. Anemia of Chronic Disease (ACD):

- It is the most common anemia in hospitalized patients.
- Pathogenesis:
 - It is a microcytic anemia.
 - It results from decreased RBC production due to impaired utilization:
 - Cytokines (IL-6, TNF) cause decreased erythropoietin (EPO) responsiveness.
 - Increased Hepcidin
 - It is an anti-microbial peptide synthesized and released by the liver.

*IDA
*ACD
*Thal
*sideroblastic

What hepcidin does:

- It inhibits release of iron from storage pools, which results in increased macrophage iron stores – “reticuloendothelial cell block”.

▪ **Causes:**

- Alcoholism – most common anemia in alcoholism
- Malignancy – most common anemia in malignancy
- Chronic inflammation:
 - Rheumatoid arthritis
 - Tuberculosis

▪ **Lab Findings:**

- Decreased MCV. — *microcytic*
- Decreased serum iron
- Decreased TIBC
- Increased serum ferritin.

IV. Sideroblastic Anemia:

- It results from defect in heme synthesis within mitochondria.

▪ **Causes:**

- Chronic alcoholism (most common) – alcohol is a mitochondrial toxin
- Pyridoxine (Vit.B6 deficiency) – most commonly from isoniazid therapy.
- Lead poisoning
- Genetic:
 - X-linked recessive.
 - Decreased δ -aminolevulinic acid synthase – the rate limiting enzyme of heme synthesis.

▪ **Lab Findings:**

- Increased serum iron
- Normal TIBC
- Increased ferritin

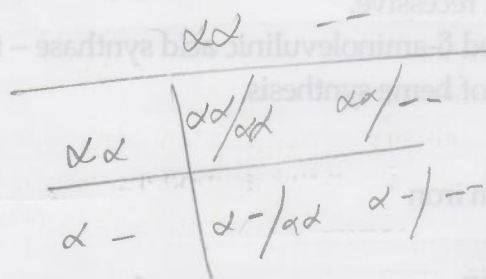
○ **Ringed Sideroblasts:**

- It refers to dark-blue granules within mitochondria – iron-laden mitochondria
- It is seen on iron stain of bone marrow.
- **RBC Basophilic Stippling** – blue dots in RBCs, seen on peripheral film.
- **RBC Pappenheimer Bodies** – iron containing inclusions, seen on peripheral film.

Microcytic Anemia (MCV < 80)

	Iron Deficiency	ACD	Thalassemia	Sideroblastic
Serum Iron (Fe)	Decreased	Decreased	Normal	Increased
TIBC	Increased	Decreased	Normal	Normal
Transferrin Saturation	Decreased	Decreased	Normal	Increased
RDW	Increased	Decreased	Normal	Normal
Serum ferritin	Decreased	Increased	Normal	Increased
Soluble transferrin receptor	Increased	Decreased	-	-

* Clinical features of β -thal major aren't evident until a/t birth b/c in fetus the γ gene is expressed from β -globin cluster. It's not until a/t birth that γ gene is turned off & β -globin gene expression begins at this time. Defective β -globin begins to cause clinical symptoms in β -thal major.



Macrocytic Anemia

- It is the group of anemia with MCV > 100.
- It is of two types:
 - **Megaloblastic Anemia:**
 - It is due to impaired DNA synthesis.
 - It is associated with hyper-segmented (> 5 lobes) neutrophils on peripheral smear.
 - It is caused by:
 - Vitamin B12 deficiency
 - Folate deficiency
 - Anti-metabolic drugs (methotrexate, 5-fluorouracil)
 - **Non-megaloblastic Anemia:**
 - It is not due to impaired DNA synthesis.
 - It is not associated with hyper-segmented neutrophils.
 - It is caused by:
 - Liver disease
 - Hypothyroidism
 - Alcoholism
 - Lesch-Nyhan syndrome

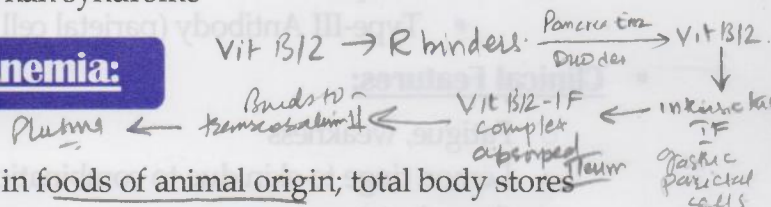
I. Vitamin B12 Deficiency Anemia:

▪ **Metabolism:**

- Vit.B12 is present only in foods of animal origin; total body stores sufficient for 2-3 years.
- Vit.B12 binds to salivary proteins called "R-binders".
- R-binders are broken down in the duodenum by the pancreatic enzymes.
- The released B12 then binds with "intrinsic factor IF", which is produced by gastric parietal cells. — *Gastroectomy*
- Vitamin B12-IF complex is reabsorbed in the terminal ileum.
- Vitamin B12 binds to transcobalamin-II and is secreted into the plasma.

▪ **Causes:**

- Decreased intake:
 - Malnutrition (elderly, alcoholism)
 - Pure vegan diet.
- Malabsorption:
 - Decreased intrinsic factor – pernicious anemia
 - Decreased gastric acid – cannot activate pepsinogen to pepsin.
 - Pancreatic insufficiency – cannot cleave R-binder



- Crohn's disease – affects terminal ileum
- Bacterial overgrowth – bacteria uses vitamin B12
- Diphyllobothrium latum – fish tapeworm

▪ Pernicious Anemia:

- atrophy gastritis
chronic inf of stomach
leading to gastric
glandular cells &
eventual replacement
by intestinal type
goblet cells
- It is an autoimmune disease characterized by atrophic gastritis.
 - It is a type-II hypersensitivity reaction.
 - It causes achlorhydria (lack HCl) and loss of gastric intrinsic factor (IF) secretion by damaging gastric parietal cells. vit B12 def
 - Incidence:
 - Slightly more common in women (> 40 years)
 - Higher incidence in if blood group A.
 - Associations:
 - Autoimmune diseases (e.g. thyroid disease, Addison's disease)
 - Increased risk (3 times) for carcinoma of the stomach.
 - Antibodies:
 - Type-I Antibody (Intrinsic Factor Antibodies)
 - It blocks binding of vitamin B-12 to intrinsic factor.
 - It is the **most specific antibody** for pernicious anemia.
 - Type-II Antibody (blocks binding of B12 – IF complex to ileal receptor)
 - Type-III Antibody (parietal cell antibodies)

▪ Clinical Features:

- Fatigue, weakness
- Lemon tinge to skin due to combination of pallor (anemia) and jaundice (hemolysis)
- Glossitis – beefy-red sore tongue
- Angular cheilosis = inflammation of corner of mouth (and lips) often then being red
- Neurological Findings:

- Peripheral neuropathy – most common
- Sub-acute Combined Degeneration (SCD) of Spinal Cord:

- ✓ ▪ Peripheral neuropathy
- ✓ ▪ Symmetrical posterior (dorsal) column loss – decreased vibratory sensation and proprioception leading to ataxia.
- Symmetrical corticospinal tract loss – spastic paralysis
- Dementia
- Classic triad = extensor plantars (UMN sign), Absent knee jerks (LMN sign), absent ankle jerks (LMN sign)

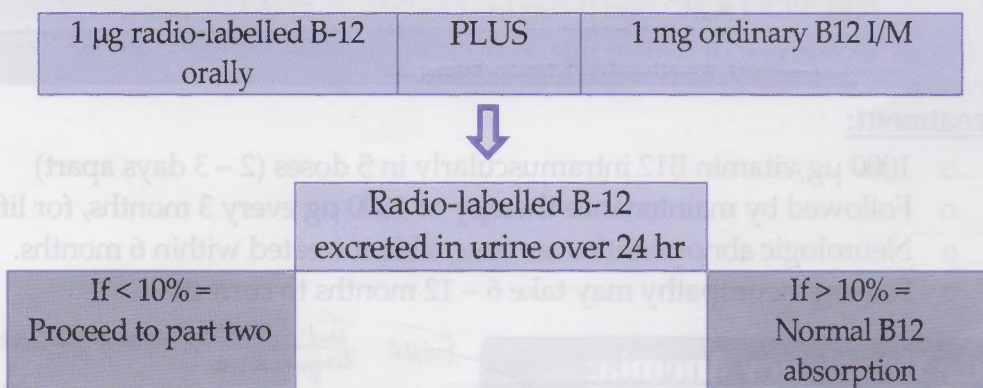
▪ **Laboratory Findings:**

- Decreased serum B12 (not reliable)
- Increased homocysteine
- Increased urine methylmalonic acid – most sensitive test
- Decreased reticulocyte count
- Increased LDH and indirect bilirubin levels.

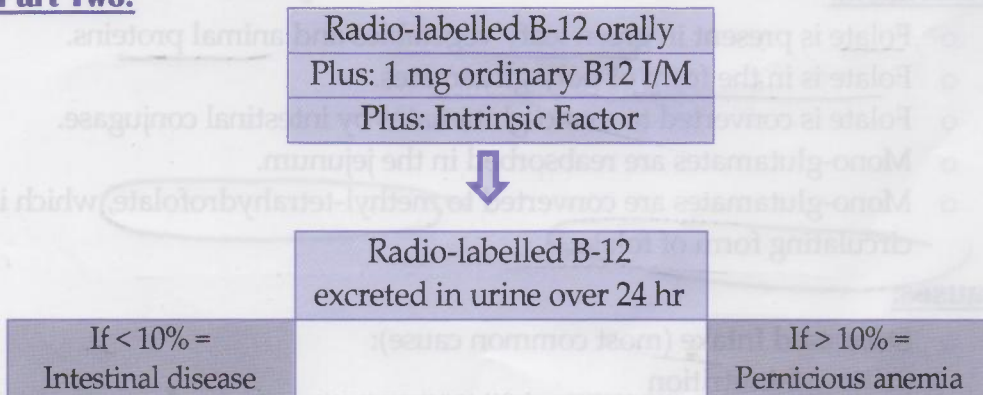
▪ **Schilling Test:**

- The finding of anti-intrinsic factor antibodies in the context of B-12 deficiency is diagnostic of pernicious anemia, without further investigations.
- However, patients with low B-12 levels but negative anti-IF antibodies should undergo Schilling test.
- Schilling test is two-part test which gives following information:
 - Whether there is B-12 Malabsorption
 - And if so, where it is occurring i.e. the site of lesion.

Part One:



Part Two:





Clinical Pearl:

B12 & Folate Deficiency:

- Vitamin B-12 and folate deficiency anemia are **both associated with same peripheral smear and bone marrow findings.**
- They are characterized by following morphologic changes:
 - 1 ○ Pancytopenia because all myeloid lineages are affected.
 - 2 ○ Anisocytosis
 - 3 ○ Macroovalocytes (RBCs are microcytic and oval)
 - 4 ○ Hyper-segmented neutrophils
 - 5 ○ Marrow hyperplasia due to increased erythropoietin
 - 6 ○ Decreased reticulocyte count.

Unlike vitamin B-12 deficiency, folate deficiency doesn't have neurologic symptoms.

- If we treat B-12 deficiency anemia with folate then folate can reverse HEMATOLOGIC abnormalities of B12 deficiency, but not NEUROLOGIC; and it can lead to "steal" of B-12 stores resulting in worsening of neurologic complications.

Exp. Iain.
Folate can treat
Hematologic
vit B12 def. prob
but not neurologic.

Treatment:

- 1000 µg vitamin B12 intramuscularly in 5 doses (2 – 3 days apart)
- Followed by maintenance therapy of 1000 µg every 3 months, for life.
- Neurologic abnormalities are reversible if treated within 6 months.
- Sensory neuropathy may take 6 – 12 months to correct.

II. Folate Deficiency Anemia:

Metabolism:

- Folate is present in green leafy vegetables and animal proteins.
- Folate is in the form of poly-glutamates.
- Folate is converted to mono-glutamates by intestinal conjugase.
- Mono-glutamates are reabsorbed in the jejunum.
- Mono-glutamates are converted to methyl-tetrahydrofolate, which is the circulating form of folate.

Folate $\xrightarrow{\text{intestinal conjugase}}$ monoglutamate
 \downarrow
 reabsorb in jejunum
 \leftarrow methyl tetrahydrofolate
 circulate

Causes:

- Decreased Intake (most common cause):
 - Malnutrition
 - Goat milk – has no folate
- Increased Demand:
 - Chronic hemolytic anemia (e.g. sickle cell disease)
 - Pregnancy

- Malignancy
- Dialysis
- Malabsorption:
 - Celiac Disease – causes folate, B12, and iron-deficiency anemia
 - Psoriasis
- Drugs:
 - 5-fluorouracil – inhibits thymidylate synthase
 - Methotrexate – inhibits dihydrofolate reductase
 - Trimethoprim-sulfamethoxazole – inhibits dihydrofolate reductase
 - Phenytoin – inhibits intestinal conjugase
- **Lab Findings:**
 - Decreased serum folate
 - Decreased RBC folate – best indicator of folate stores
 - Increased homocysteine
 - NORMAL urine methylmalonic acid
 - Decreased reticulocyte count
 - Increased LDH and indirect bilirubin levels.

Same

Clinical Pearl:**Megaloblastic Anemia:**

- Vitamin B12 deficiency anemia :
 - Elevated methylmalonic acid
 - Elevated homocysteine
 - Folate deficiency anemia:
 - Normal methylmalonic acid
 - Elevated homocysteine
- **Treatment:**
- Oral folic acid 5 mg daily for 3 weeks.
 - Followed by maintenance therapy of 5 mg once weekly.

Normocytic Anemia

Basic def:

- It is a group of anemias with normal MCV i.e. between 80 – 100 fL.

Hemolytic Anemias:

- Intrinsic hemolytic anemia refers to a defect in the RBC causing the anemia.
- Extrinsic hemolytic anemia refers to factors outside the RBC causing hemolysis.
- Hemolytic anemias may be of following types:

(i). Extravascular Hemolysis:

- It is characterized by breakdown of RBCs in the reticuloendothelial system i.e. macrophages of spleen (most common site), liver, and bone marrow.

Lab Findings:

- 10 Anemia

- 20 Increased reticulocytes (> 2%) — *why*

- 30 Jaundice – unconjugated hyperbilirubinemia = *why*

- 40 Splenomegaly — *why* whenever any disease cause prod. of ab-RBC — those lysis — cause it

- 50 Increased LDH from hemolyzed RBCs *Lactate dehydrogenase*

(ii). Intravascular Hemolysis:

- It is characterized by breakdown of RBCs in the circulation (within the blood vessels)

Lab Findings:

- Anemia and increased reticulocyte count.

- Hemoglobinemia — increased free plasma hemoglobin

- Hemoglobinuria — red brown urine in the absence of red blood cells.

- Hemosideruria *Hemosiderin → urine*

- Methemalbuminemia — combination of heme with albumin

- Decreased serum haptoglobin

Clinical Pearl:

Hemolytic Anemia:

- Always suspect hemolytic anemia when laboratory findings show:
 - Increased RBC production = increased reticulocyte count
 - Increased RBC breakdown:
 1. Anemia
 2. Increased serum bilirubin (indirect)
 3. Increased LDH
 4. Increased urobilinogen
 5. Decreased plasma haptoglobin

I. Hereditary Spherocytosis (HS):

- It is an autosomal dominant disorder, with intrinsic defect and extravascular hemolysis.
- It is normocytic anemia with high reticulocyte count.
- Pathogenesis:**
 - It is due a defect in membrane protein that makes the RBCs spheroid, less deformable, and vulnerable to splenic sequestration and destruction.

The most common mutations associated with HS are in:

- Ankyrin (most common)
- Beta spectrin
- Band-3
- Band-4

what funct.

Life span becomes of spherocytic RBC = 10-20 days

Clinical Features:

- Recurrent episodes of hemolysis
- Intermittent jaundice
 - Positive family history
 - Moderate splenomegaly (500 – 1000 gm)
 - Pigment (black) gallstones (50%)
 - Crisis:

There's also loss of K^+ & H_2O along with RBC causing dehydration &

- Hemolytic crisis:
 - Hemolysis increases and becomes more severe
 - Associated with infection

occurs when large # of RBC are destroyed over a short time - loss of RBC occurs much faster than your body can produce new cells.

- Aplastic crisis:
 - Severe anemia & low reticulocyte count
 - Caused by parvovirus B19.

Failure of bone marrow to produce any red blood cells.

- Megaloblastic crisis:
 - Occurs due to folate deficiency,
 - Often the first presentation of disease in pregnancy

Diagnostic Tests:

- Spherocytes:
 - Spherocytes are seen on peripheral film.
 - Spherocytes are small, dark-staining red cells with NO central areas of pallor.

① peripheral film.

- Increased MCHC – responsible for loss of central area of pallor. due to loss of H_2O & potassium
- Negative Coomb's test.
- Osmotic Fragility Test = Spherocytes rupture in hypotonic salt solution.

usually.

R_X

Treatment:

- Chronic folic acid replacement – 5 mg daily for life.
- Splenectomy:
 - It improves, but does not normalize red cell survival.
 - Indication – moderate to severe hemolysis.
 - It should be delayed until after 6 years of age – risk of sepsis.
 - Immunization:
 - Elective cases – give vaccine 2 – 3 weeks prior to splenectomy
 - Emergency cases – give vaccine after surgery (less effective).
 - Vaccines:
 - Pneumococcal, hemophilus influenzae type-B,
 - Meningococcal group C, influenza

*Polycy-
themia
in which
over - folic acid
5mg/den
3 weeks
for*

II. Sickle Cell Disease:

- It is an autosomal recessive disorder, with intrinsic defect and extravascular hemolysis.
- It is a type of normocytic anemia with high reticulocyte count. *same*

Genetics:

- It is caused by a point mutation at position 6 of the β -globin chain resulting in substitution of valine for glutamic acid.
- Heterozygous Condition:
 - It is known as Sickle cell trait i.e. HbAS.
 - It contains 60% normal Hb, and 40% is sickle Hb (HbS).
 - It produces no anemia.
 - Protective against falciparum malaria.
- Homozygous Condition:
 - It is known as Sickle cell anemia i.e. HbSS.
 - It contains 100% HbS, with no normal Hb.
 - It produces anemia.
 - Not protective against falciparum malaria.

Pathogenesis:

- HbS when deoxygenated undergoes aggregation and polymerization.
- HbS polymerization causes RBCs to assume a sickle shape and decrease RBC deformability, resulting in hemolysis and microvascular occlusion.
- Sickling is precipitated by hypoxia, acidosis, dehydration, and infection.
- Early stages = splenomegaly

*Point mut., #6
in globin chain gene
valine instead of glutamic acid*

- Late stages = **Auto-splenectomy** (due to erythrostasis leading to tissue hypoxia and infarction)

Clinical Findings:

(i). Susceptibility to Infections:

- It is due to dysfunctional spleen and impairment of opsonization of encapsulated bacteria.
- Most common are:
 - **Septicemia = strep. pneumoniae (most common cause of death in children)**
 - Meningitis = streptococcus pneumoniae and Hemophilus Influenzae
 - **Osteomyelitis = most commonly by Salmonella.**

(ii). Vaso-occlusive Crises:

- **It is the most common crisis in sickle cell anemia.**
- It results from microvascular occlusion.
- It causes
 - Stroke
 - Mesenteric ischemia
 - Avascular necrosis of femoral head.
 - Priapism – prolonged painful erection
 - **Hand-Foot Syndrome (Dactylitis)**
 - It is the most common presentation in infants.
 - It presents with painful swelling of hands and feet due to bone infarctions.
 - **Acute Chest Syndrome:**
 - **Most common cause of death in adults.**
 - Vaso-occlusion of pulmonary capillaries
 - Presents with chest pain, shortness of breath, wheezing, hypoxemia and infiltrates on chest x-ray.

(iii). Aplastic Crises:

- It is caused by parvovirus B19 resulting in cessation of bone marrow erythropoiesis.
- **Reticulocytopenia (decreased reticulocyte count) – only condition in sickle cell anemia in which the reticulocyte count is low.**
- Sudden and rapid worsening anemia.
- Decreased platelets

(iv). Sequestration Crises:

- It mainly affects children with functional spleen.
- Splenomegaly due to entrapment of RBCs.
- Reticulocytosis (increased reticulocyte count)
- Increased platelets.

■ Lab Diagnosis:

- CBC = normocytic anemia with raised reticulocyte count.
- Peripheral film:
 - Sickle cells
 - **Howell – Jolly bodies** (which are nuclear remnants of RBCs)
- Sickling Test:
 - Metabisulfite, an O₂-consuming reagent is used.
 - It reduces O₂ tension, and induces sickling.
 - It can't differentiate sickle cell anemia from sickle cell trait.
- Hb Electrophoresis:
 - **It is the most accurate test.**
 - HbAS profile = HbA 60%, HbS 40%
 - HbSS profile = HbS 95%, HbF 5%, HbA 0%.
 - Both parents of affected individual will have sickle cell trait.

R_x

Treatment:

○ **Vaso-occlusive crisis:**

- Aggressive rehydration
- Oxygen therapy
- Analgesia
- Antibiotics
- **Hydroxyurea:**
 - It is used in treatment of this disease.
 - It increases HbF and prevents sickling.
 - It can form NO, a vasodilator.
 - It prevents red cells stasis due to its anti-inflammatory effect.

○ **Prophylaxis:**

- Folic acid supplementation
- Penicillin V (protects against pneumococcal infection)
- Vaccination against encapsulated organisms:
 - Encapsulated organisms – pneumococcal, meningococcal, H. influenzae
 - Hepatitis B vaccination

○ **Exchange Transfusion:**

- It means that the patient is simultaneously venesected and transfused to replace HbS with HbA.
- It is indicated in following conditions:
 - Acute chest syndrome
 - Priapism
 - Stroke
 - Visual disturbance from retinal infarction



Clinical Pearl:

Sickle Cell Anemia:

- Howell-Jolly bodies indicate splenic dysfunction.
- Howell-Jolly bodies have no clinical significance, as their presence doesn't alter the management.
- In sickle-cell anemia, hemoglobin binds to and inactivates nitric oxide (NO), resulting in vasoconstriction and platelet aggregation.
- These findings provide rationale for NO therapy in sickle cell anemia.

III. Glucose-6-Phosphage Dehydrogenase (G6PD) Deficiency:

- It is X-linked recessive disorder; therefore it affects only males.
- It is due to intrinsic defect and episodic primary intravascular and secondary extravascular hemolysis.
- It is normocytic anemia with high reticulocyte count.

▪ **Pathogenesis:**

(i). Normal:

- G6PD is the rate-limiting enzyme in hexose-monophosphate shunt (HMP).
- G6PD normally produces NADPH, which keeps glutathione reduced (GSH).
- GSH protects RBCs by breaking down hydrogen peroxide.

(ii). Deficiency:

- G6PD deficiency results in decreased NADPH, and consequently decreased GSH.
- GSH deficiency causes hydrogen peroxide to oxidize Hb, which precipitates in the form of Heinz bodies.
- **Heinz bodies** damage RBC membranes causing intravascular hemolysis.
- Heinz bodies removed from RBC membrane by splenic macrophages produce "Bite Cells".

▪ **Clinical Features:**

- Sudden anemia and jaundice in men of African or Mediterranean origin.
- Anemia is triggered by oxidative stress, e.g.:
 - Infections (most common), e.g. viral hepatitis
 - Drugs – primaquine, dapsone, sulfonamides, methylene blue
 - Diabetic ketoacidosis (DKA)
 - Foods – fava beans in children

▪ **Diagnostic Test:**

- CBC:
 - Normocytic, hemolytic anemia
 - Increased reticulocyte count.
- Peripheral film:
 - **"Bite Cells"** (RBCs with a bite of membrane missing)
 - **"Heinz – Bodies"** (denatured hemoglobin)
- Most accurate test:
 - Enzyme (G6PD) level
 - It may be normal during active disease.
 - It is therefore performed when hemolysis subsides after 1 to 2 months

R_x

Treatment:

- Stop any offending drugs.
- Treat underlying infection
- Blood transfusion may be life-saving
- Splenectomy is NOT usually helpful

IV. Autoimmune Hemolytic Anemia (AIHA):

- It is a group of extrinsic hemolytic anemias with extravascular or intravascular hemolysis.
- Lab Findings in AIHA:
 - Positive Coomb's test
 - Micro-spherocytes
 - Normocytic anemia
 - High reticulocyte count

(i). Warm Antibody AIHA:

- It is the most common immune hemolytic anemia (70%) and IgG-mediated.
- It doesn't usually fix the complement.
- It is active at 37° C.

▪ **Causes:**

- Idiopathic (most common)
- SLE – most common known cause
- Lymphomas and leukemia
- Drugs – penicillin, rifampin, phenytoin

▪ **Mechanism:**

- RBCs coated with IgG are phagocytosed by splenic macrophages.
- It is therefore extravascular hemolysis; forms spherocytes.
- **Difference from hereditary spherocytosis:**
 - No positive family history
 - Positive Coomb's test.

R_x

Treatment:

- Corticosteroids (prednisolone) – best initial therapy
- Acute episode not responding to steroids = intravenous immunoglobulin (IVIG)
- Recurrent episodes, despite being on steroids:
 - Splenectomy, OR
 - Immunosuppressive therapy (azathioprine, cyclophosphamide)
- Rituximab (anti-CD20 monoclonal antibody) is used when splenectomy does not control the hemolysis.

(ii). Cold Agglutinin Disease:

- It is less common (30%) and IgM-mediated.
- It fixes complement in peripheral cool parts of body (finger, toes)
- It is active at 0° to 4°C, and dissociates at 30°C and above.

▪ **Causes:**

- Idiopathic
- Mycoplasma infection
- Infectious mononucleosis
- Lymphoma
- Waldenstrom macroglobulinemia

▪ **Presentation:**

- Chronic anemia made worse by cold.
- Numbness and mottling of nose, ears, fingers and toes.
- Raynaud's phenomenon
- Symptoms resolve on warming up the body part.

▪ **Diagnosis:**

- Standard Coomb's test = negative
- Complement test = positive

R_x

Management:

- Stay warm
- Rituximab
- Immunosuppressants, e.g. cyclophosphamide, cyclosporine
- Steroids and splenectomy have no role (unlike warm-type)

V. Paroxysmal Nocturnal Hemoglobinuria (PNH):

- It is the only hemolytic anemia caused by an "acquired" intrinsic defect in the cell membrane.
- It results in anemia due to complement over-activation.

▪ **Pathogenesis:**

- It is caused by acquired mutations in phosphatidylinositol glycan A (PIGA), required for synthesis of glycosylphosphatidylinositol (GPI) anchors.
- GPI inactivates complement, therefore their absence in PNH results in complement destruction of hematopoietic cells.
- GPI-linked proteins that regulate complement activity are (& are deficient in PNH):
 - C8 binding protein
 - **CD 55** = decay accelerating factor
 - **CD 59** = membrane inhibitor of reactive lysis
 - It is the most important GPI-linked protein.
 - It is a potent inhibitor of C3 convertase.
 - It therefore prevents spontaneous activation of alternative complement pathway.

▪ **Clinical features:**

- Intravascular hemolysis, which is paroxysmal and nocturnal (25%)
- Chronic hemolysis, without dramatic hemoglobinuria (75%)
- Pancytopenia (anemia, leucopenia, and thrombocytopenia)
- Episodic thrombosis (venous > arterial):
 - It is severe, but inconstant complication of the disease.
 - **It is the most common cause of death**
 - It results in hepatic, portal, and cerebral vein thrombosis.
 - It is fatal in 50% of cases.

▪ **Lab Findings:**

- Flow Cytometry:
 - **Peripheral blood flow Cytometry is the most accurate test.**
 - Flow Cytometry shows decreased CD 55 and 59.
- Sugar water test:
 - Sucrose hemolysis test is the screening test.
 - Sucrose enhances complement destruction of RBCs.
- Ham's test:
 - It is confirmatory test.
 - Acidified serum activates the alternative pathway causing hemolysis.

R_x

Management:

- Prednisolone
- Allogeneic bone marrow transplantation – only method of cure
- **Eculizumab** – inactivates C5 in the complement pathway and decreases hemolysis.
- Supportive care i.e. iron, folate, and transfusion.

VI. Aplastic Anemia:

- It is normocytic anemia with low reticulocyte count.
- It results most commonly from suppression of stem cell function by activated T cells
- **Causes:**
 - Idiopathic = most common
 - Inherited = Fanconi anemia
 - Drugs :
 - Most common known cause.
 - Alkylating agents
 - Chloramphenicol
 - Streptomycin
 - Infections:
 - Cytomegalovirus
 - Epstein-Barr virus
 - Hepatitis
 - Varicella Zoster
- **Clinical Findings:**
 - Anemia = weakness
 - Neutropenia = infection

- Thrombocytopenia = bleeding
- Splenomegaly is characteristically absent.
- Diagnosis:
 - CBC = pancytopenia
 - Bone marrow biopsy:
 - It is the most accurate method.
 - It shows hypocellularity, and contain fat cells

R_x

Treatment:

- Supportive:
 - Anemia = blood transfusion
 - Infection = antibiotics
 - Bleeding = platelets
- Young patients (< 30 years) = allogeneic bone marrow transplantation is curative
- Old patients = immunosuppressive therapy with cyclosporin and anti-thymocyte globulin

Bleeding Disorders

Tests for Hemostasis:

- **Bleeding Time:**
 - It measures time taken for a standardized skin puncture to stop bleeding.
 - It varies from 2 – 9 minutes (average is < 8 minutes)
- **Platelet Count:**
 - It ranges from 150 – 300 × 10³/μL
 - Normal count does not guarantee normal platelet function.
- **Prothrombin Time (PT):**
 - Normal reference interval = 9 – 12 seconds.
 - It is a test of **extrinsic** and common coagulation pathway.
 - Extrinsic Factor = factor VII
 - Common Factors = X, V, II (prothrombin), and I.
- **Partial Thromboplastin Time (PTT):**
 - Normal reference interval = 26 – 36 seconds.
 - It is a test of **intrinsic** and common coagulation pathway.
 - Intrinsic Factors = factor XII, XI, IX, VIII
 - Common factors = X, V, II (prothrombin), and I.

	<u>Platelet Defects</u>	<u>Coagulation Defects</u>
Site of bleeding	Superficial (e.g. skin and mucous membranes)	Deep (e.g. muscle and joints)
Lesions	Petechiae, ecchymosis	Hemarthroses, hematomas
Bleeding	After minor cuts: Yes After surgery: immediate, mild	After minor cuts: Unusual After surgery: delayed, severe

Platelet Disorders:

I. Idiopathic Thrombocytopenic Purpura (ITP):

- It is a disease caused by IgG antibodies against Glycoprotein IIb/IIIa receptors.
- It is an isolated thrombocytopenia; hematocrit and WBC count are normal.
- Spleen is normal-sized.
 - Primary ITP = ITP occurring in the absence of any known risk factors
 - Secondary ITP = ITP associated with other diseases or drug exposure.
- **Lab Findings:**
 - Smear = micro-spherocytes
 - Coomb's test is positive

- PT and APTT = Normal
- Bleeding Time = Prolonged
- Bone Marrow biopsy = increased number of megakaryocytes.

	<u>Acute ITP</u>	<u>Chronic ITP</u>
Age	Most common cause of thrombocytopenia in children 2 – 6 years of age.	Most common cause of thrombocytopenia in adults.
Sex	No sex predilection	More common in women (20 – 40 years)
Onset	Abrupt, 1 – 3 weeks after a viral infection.	Insidious onset.
Treatment	Responds well to steroids	Often resistant to steroids

Rx

Management:

- No bleeding, platelet count > 30,000 = no treatment
- Mild bleeding, platelet count < 30,000 = glucocorticoids
- Severe bleeding (CNS or GI), count < 10,000:
 - Glucocorticoids, PLUS:
 - Intravenous immunoglobulin (IVIG) – OR:
 - Intravenous Anti-Rh (D) in Rh-positive individuals.
- Splenectomy:
 - Indications – chronic, refractory disease (> 6 months), ≥ 2 relapses.
 - Complete remission in 70% cases (only 5 – 10% require further medical therapy)
 - Splenectomy not effective in controlling bleeding.
- Second-Line Therapy:
 - It is indicated in patients with persistent disease despite splenectomy.
 - Options:
 - “Romiplostim” – thrombopoietin analogue
 - “Eltrombopag” – thrombopoietin receptor agonist
 - Rituximab
 - Azathioprine
 - Cyclosporine
 - Mycophenolate

II. Thrombotic Thrombocytopenic Purpura (TTP):

- It is a vascular occlusive disease with **systemic platelet aggregation**.
- **Pathogenesis:**
 - Deficiency of enzyme **ADAMTS-13** (also called vWF-cleaving metalloprotease).
 - ADAMTS-13 is required for the breakdown of high molecular weight multimers of von Willebrand factor (vWF).
 - Deficiency of this enzyme results in accumulation of multimers of vWF in the plasma and systemic platelet aggregation.
- **Lab Findings:**
 - Smear = Schistocytes
 - Coomb's test is negative
 - PT and APTT = Normal
 - Bleeding Time = Prolonged
- **Clinical Features (TTP Pentad):**
 - Thrombocytopenia
 - Microangiopathic hemolytic anemia (MHA):
 - Normocytic anemia
 - Increased LDH
 - Increased indirect bilirubin
 - Schistocytes – sign of MHA
 - Renal failure
 - Fever
 - CNS deficits
- **Management:**
 - Urgent plasma exchange (Plasmapheresis)
 - Glucocorticoids
 - Fresh frozen plasma – if there is delay to perform plasma exchange
 - **Platelet transfusion is contraindicated – increases microvascular thrombosis**

III. Hemolytic Uremic Syndrome (HUS):

- It is a vascular occlusive disease with **intra-renal aggregation**.
- **Pathogenesis:**
 - Mediator is Shiga-like toxin of O157: H7 serotype of entero-hemorrhagic *E. coli*.

- Shiga-toxin binds and activates renal endothelial cells and platelets resulting in intra-renal thrombi formation.
- **Lab Findings:**
 - Smear = Schistocytes
 - Coomb's test is negative
 - PT and APTT = Normal
 - Bleeding Time = Prolonged
- **Clinical Features (HUS Triad):**
 - Thrombocytopenia
 - Renal failure
 - Microangiopathic hemolytic anemia (MHA):
 - Normocytic anemia
 - Increased LDH
 - Increased indirect bilirubin
 - Schistocytes – sign of MHA
 - It affects children.
 - It is associated with prodrome of bloody diarrhea caused by E.coli
- **Management:**
 - Urgent plasma exchange (Plasmapheresis)
 - Glucocorticoids
 - Fresh frozen plasma – if there is delay to perform plasma exchange
 - Platelet transfusion is contraindicated – increases microvascular thrombosis
 - Antibiotics are contraindicated too.

IV. Heparin-Induced Thrombocytopenia (HIT):

- It is the most common cause of thrombocytopenia in hospitalized patients.
- It should be suspected in patients on heparin therapy:
 - With > 50% decrease in platelet count from the baseline
 - Even if the count remains above 150,000.
- Pathogenesis:
 - Type-I HIT:
 - It is non-immune; caused by direct effect of heparin.
 - Incidence is 10 – 20%
 - Onset = 1 – 4 days of heparin therapy
 - Platelet nadir = > 100,000/ μ l.
 - Complication = none
 - Management = can continue heparin, with close observation.

- Type-II HIT:
 - It is type-II hypersensitivity; IgG antibodies against **platelet factor 4** – heparin complex.
 - Incidence is more with unfractionated heparin than LMWH.
 - **Onset = 5 – 14 days of heparin therapy**
 - **Platelet nadir = decrease by more than 50%.**
 - Complications = thrombosis (**venous thrombosis** > arterial thrombosis)
 - Management:
 - Discontinue ALL forms of heparin
 - Start direct thrombin inhibitors – Argatroban, Lepirudin, Bivalirudin,
 - Once platelet count is > 150,000 start warfarin.

Coagulation Disorders:

I. Von Willebrand Disease (vWD):

- It is an autosomal dominant disorder; gene for vWF is located on chromosome 12.
- It is the most common inherited bleeding disorder.
- Von Willebrand factor (vWF) normally performs following functions:
 - It brings platelets into contact with exposed endothelium.
 - It makes platelets bind to each other.
 - It binds to factor VIII, protecting it from destruction in circulation.
 - It therefore acts as platelet glue and plasma carrier of factor VIII.
- **Pathogenesis:**
 - It is characterized by decreased in the level or functioning of vWF.
 - Deficiency of vWF results in:
 - Decreased factor-VIII – due to loss of protective effect
 - Dysfunctional platelets, although the count is normal.
- **Types:**
 - Type-I = it accounts for (70%) and is autosomal dominant.
 - Type-2 = it accounts for 25% and is autosomal dominant.
 - Type-3 = it is autosomal recessive, caused by gene deletions.
- **Lab Findings:**
 - Platelet count = Normal but defected.
 - Bleeding Time = Increased
 - PT = Normal

- PTT = Increased (due to decreased factor VIII)
- vWF activity = decreased (measured by ristocetin cofactor assay).
- Confirmation = **vWF multimer analysis**

R_x

Management:

- Mild Bleeding:
 - Desmopressin (DDAVP) – increases endothelial cell release of vWF.
 - Tranexamic acid may be useful in mucosal bleeding.
- Severe Bleeding:
 - vWF replacement:
 - Cryoprecipitate
 - Factor VIII concentrate rich in vWF
 - Recombinant vWF.
 - Bleeding in type-3 patients responds to nothing apart from concentrates.

II. Hemophilia A:

- It is the most common congenital coagulation factor deficiency.
- It is caused by a reduction in the amount or activity of factor VIII.
- It is X-linked recessive, and thus occurs in males, while females are asymptomatic carriers.
- Hemophilia B (Christmas disease) is due to factor IX deficiency.
- Classification:
 - Severe disease = less than 1% of normal factor VIII activity
 - Moderate disease = 2 – 5% of normal factor VIII activity
 - Mild disease = 6 – 50% of normal factor VIII activity.
- Clinical Findings:
 - Spontaneous hemorrhages (mucous membrane, GI, GU)
 - Hemarthroses i.e. bleeding into joints after trauma
 - Muscle hematomas – most commonly in the calf and psoas muscles
 - Petechiae are characteristically absent.
 - Crippling arthropathy
- Lab findings:
 - Platelet count = Normal
 - BT = Normal
 - PT = Normal
 - PTT = Increased

▪ **Management:**

- Mild Cases = Desmopressin (DDAVP)
- Severe Cases = Recombinant factor VIII.
- Hemophilia B = Recombinant factor IX.

III. Disseminated Intravascular Coagulation (DIC):

- It is a thrombo-hemorrhagic disorder.

▪ **Pathogenesis:**

- Massive activation of coagulation that overwhelms control mechanisms.
- Thrombosis in microvasculature leading to ischemia and microangiopathic hemolytic anemia.
- Acute DIC causes consumption of coagulation factors and platelets leading to **bleeding**.
- Chronic DIC causes repletion of coagulation factors and platelets leading to **thrombosis**.

▪ **Causes:**

- Sepsis (most common):
 - E. coli
 - Neisseria meningitides.
- Obstetric complications:
 - Placental abruption
 - Septic abortion
- Malignancy:
 - Carcinoma of pancreas, prostate, lung, and stomach
 - Acute promyelocytic (M3) leukemia
- Major trauma:
 - Crush injuries
 - Burns, extensive surgery

▪ **Clinical Course:**

- Bleeding is common in acute DIC, as in obstetric complications.
- Thrombotic complication is common in chronic DIC, as in malignancy.
- Microangiopathic hemolytic anemia.
- Thrombi found in:
 - Brain (most common)
 - Heart; Lungs; Kidneys

▪ **Lab Findings:**

- Platelet count = Decreased
- BT = Increased
- PT = Increased
- PTT = Increased
- Fibrinogen = decreased
- D-dimer = increased
- FDPs = increased (FDPs = fibrin degradation products)

R_x

Management:

- Treat the underlying cause
- Supportive treatment:
 - Fresh frozen plasma
 - Cryoprecipitate
 - Platelets
 - Consider activated protein C in severe sepsis

Leukemias:

- Leukemias are malignant disorders of the hematopoietic stem cell compartment, characteristically associated with increased number of white cells in the bone marrow and/or peripheral blood.
- **Acute leukemia:**
 - Abrupt onset of bone marrow failure (i.e. anemia, infection, and bleeding).
 - Failure of cell maturation, resulting in increased blast cells of > 20% in bone marrow.
 - Acute leukemias are:
 - Acute Lymphoblastic Leukemia (ALL)
 - Acute Myelogenous Leukemia (AML)
- **Chronic leukemia:**
 - Insidious onset of bone marrow failure.
 - Blast cells are < 20% in bone marrow.
 - Chronic leukemias are:
 - Chronic Lymphocytic leukemia (CLL)
 - Chronic Myeloid Leukemia (CML)

*clonal cell → d/f .
↓
mature ← replicate*

I. Acute Lymphoblastic Leukemia (ALL):

- **Introduction:**
 - ALL is a group of neoplasms composed immature, precursor B or T lymphocytes referred to as "Lymphoblasts".
 - ALL is the most common leukemia in children (newborn to 14 years of age).
- **Types:**

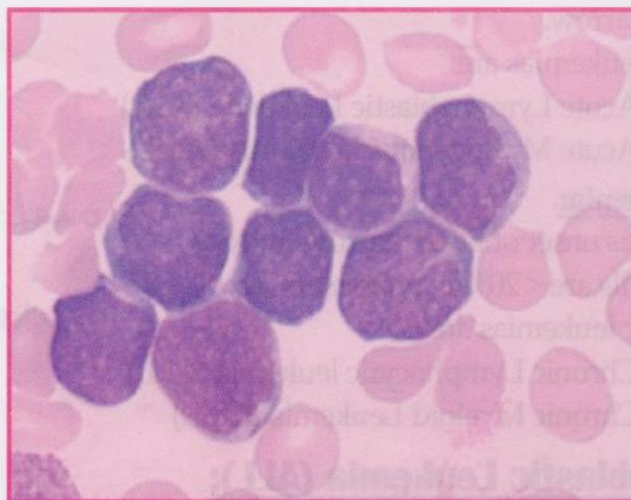
	<u>Precursor B-cell ALL</u>	<u>Precursor T-cell ALL</u>
1	It accounts for 85% of ALL	It accounts for 15% of ALL.
2	It is predominantly present in children.	It is predominantly present in adolescents.
3	It presents with pancytopenia.	It presents with thymic masses.
4	Commonly metastasize to CNS and testes ("Sanctuary site")	Not common
5	Deoxynucleotidyltransferase (TdT) positive (95%).	Deoxynucleotidyltransferase (TdT) positive (95%)

▪ Clinical Findings:

- Abrupt stormy onset of symptoms → 5 wks
- Generalized lymphadenopathy →
- Splenomegaly and hepatomegaly → may
- Bone pain and tenderness → may
- **CNS involvement:** cranial neuropathies, nausea, vomiting, headache
- Pancytopenia
 - Anemia = fatigue, weakness
 - Neutropenia = infection
 - Thrombocytopenia = bleeding — Plat — Tru



Prophylactic
chemo



ALL: Lymphoblasts

▪ Lab Findings:

- WBC-count 10,000 – 100,000 cells.
- Bone marrow often totally replaced by lymphoblast.
- Normocytic anemia and thrombocytopenia
- Bone marrow biopsy:
 - > 20% lymphoblasts in bone marrow.
 - Lymphoblasts have agranular cytoplasm (granules are seen in AML)
 - Lymphoblasts are **PAS-positive** (periodic acid-Schiff), **CALLA positive**, and **TdT positive**.

▪ Poor Prognosis:

- Age < 2 or > 10 years
- Presentation in adolescence
- WBC > 100,000/cmm³
- Presence of Philadelphia chromosome (t(9;22))

Terminal deoxynucleotidyl transferase
a DNA polymerase expressed only
by pre B or T lymphoblast
present in > 95% cases

Translocation

from 9 → 22

II. Acute Myelogenous Leukemia (AML):

- It is the most common leukemia of adults.
- **Clinical Features:**
 - Marrow Failure:
 - Anemia
 - Infection
 - Bleeding
 - Infiltration:
 - Hepatosplenomegaly
 - Gum infiltration
 - ~~CNS involvement is rare (unlike ALL)~~
- **Classification:**

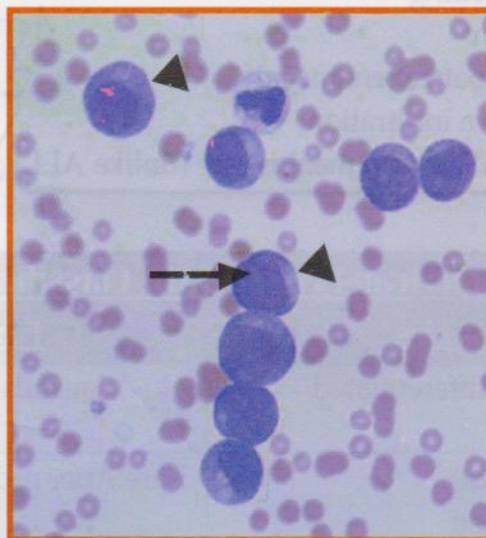
ALL / AML
 Children / Adult
 Lymphoid lineage / Myeloid lineage
 CNS involved / Not involved (Rare)
 Hepato Splenomegaly
 Agranular / Granular
 Leukemia

French-American-British (FAB) Classification of AML:

	Class	Features
M0	Minimally differentiated AML	No Auer rods
M1	AML without differentiation	Rare Auer rods
M2	AML with maturation	Most common type (30 – 40%) Auer rods present t(8:21) translocation
M3	Acute promyelocytic	Auer rods present t(15:17) translocation DIC present (bleeding diathesis)
M4	Acute myelomonocytic	Auer rods uncommon Inversion inv(16) = better prognosis
M5	Acute monocytic	Auer rods absent Gum infiltration Organomegaly, lymphadenopathy
M6	Acute erythroleukemia	Bizarre multinucleated erythroblast
M7	Acute megakaryocytic	Myelofibrosis in bone marrow Increased incidence in Down syndrome in children < 3 years

- **Lab Findings:**
 - WBC-count 10,000 – 100,000 cells.
 - Bone marrow biopsy:
 - > 20% myeloblast in bone marrow.

- Myeloblasts have granular cytoplasm
- Myeloblasts are **myeloperoxidase positive**, and **Sudan black positive**.
- **Auer rods:**
 - These are fused azurophilic granules in cytoplasm of myeloblasts.
 - These are characteristic feature of AML.



AML: Arrow Head = Myeloblast
Arrow = Auer Rod

- **Prognosis:**
 - Good prognosis:
 - Promyelocytic leukemia (M3)
 - t(8:21) and t(15:17)
 - inv(16)
 - Poor Prognosis:
 - Age > 60 years
 - Cytogenetic abnormalities
 - -5, -7, deletion
 - 3q26 aberrations

Rx

Treatment of Acute Leukemia:

○ Chemotherapy:

- Remission Induction = this phase destroys the bulk of tumor by combination chemotherapy.
- Remission Consolidation = this phase attacks the residual disease once remission has been achieved.
- Remission Maintenance = this phase involves maintenance therapy using a repeating cycle of drug administration to keep patient in remission.

Phase	ALL	AML
Induction	<ul style="list-style-type: none"> ▪ Vincristine ▪ Prednisolone ▪ Cyclophosphamide ▪ Anthracycline ▪ Asparaginase ▪ CNS prophylaxis: <ul style="list-style-type: none"> ○ Intrathecal methotrexate ○ Intracranial radiotherapy 	<ul style="list-style-type: none"> ▪ Duanorubicin ▪ Cytarabine ▪ Etoposide ▪ NO CNS prophylaxis
Consolidation	<ul style="list-style-type: none"> ▪ Duanorubicin ▪ Cytarabine ▪ Etoposide ▪ Methotrexate 	<ul style="list-style-type: none"> ▪ Cytarabine ▪ Amsacrine ▪ Mitoxantrone
Maintenance	<ul style="list-style-type: none"> ▪ Prednisolone ▪ Vincristine ▪ Mercaptopurine ▪ Methotrexate 	

○ Supportive Care:

- Anemia = blood transfusion (keep Hb > 10g/dL)
- Bleeding:
 - Non-infected patient = give platelets when count is < 10, 000.
 - Infected patient = give platelets when count is < 20, 000.
- Infection:
 - Antibiotics

- Aminoglycoside (gentamicin) + broad spectrum penicillin (piperacillin/tazobactam)
- Fever ($> 38^{\circ}\text{C}$) lasting > 1 hour in a neutropenic patient indicates possible septicemia.
- Fungal Infections:
 - Local infections = fluconazole
 - Systemic infection = intravenous amphotericin for at least 3 weeks
- **Tumor Lysis Syndrome:**
 - It is a syndrome caused by cellular breakdown during chemotherapy.
 - It is characterized by:
 - Hyperkalemia
 - Hyperphosphatemia
 - Hyperuricemia
 - Hypocalcemia
 - It is prevented by:
 - Intravenous hydration
 - Prophylactic allopurinol



Clinical Pearl:

Acute Promyelocytic Leukemia (APL)

- It is M3-AML (see table above FAB classification)
- It is defined by translocation of retinoic acid receptor: $t(15:17)$; PML—RAR α
- It may present as medical emergency with **DIC and bleeding**.
- Treatment:
 - Supportive care measures are crucial
 - **All-trans retinoic acid** (ATRA) – remarkable response
 - Arsenic trioxide (ATO)

III. Chronic Lymphocytic Leukemia (CLL):

- CLL is a clonal proliferation of normal mature-appearing B-lymphocytes that function abnormally.
- **Epidemiology:**
 - It occurs in individuals > 60 years.
 - **It is the most common overall leukemia**

- It is the most common cause of generalized lymphadenopathy in people > 60 years.

• Clinical Features:

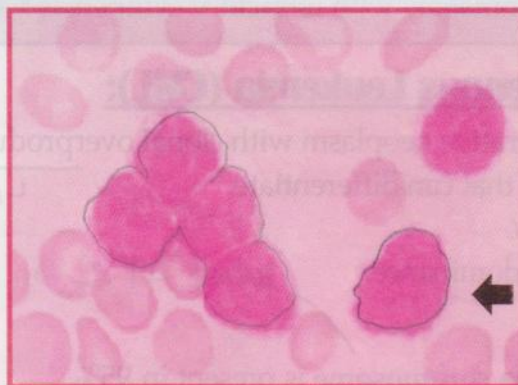
- **Fatigue – most common symptom**
- Lymphadenopathy Generalized
- Spleen or liver enlargement (hepatosplenomegaly)
- Infection
- Autoimmune hemolytic anemia and thrombocytopenia
- **Richter's syndrome:** 5–10% cases Pt

(2)

- It refers to transformation of CLL into more aggressive form.
- It takes the form of diffuse large B-cell lymphoma.

• Diagnosis:

- Lab Findings:
 - WBC-count = lymphocytosis (>5000, mature-appearing small cells)
 - Lymphoblast < 10%.
- Bone marrow biopsy:
 - Spherocytes – from autoimmune hemolytic anemia ✓
 - **Smudge Cells** ("parachute cells"): ← Peripheral Blood Film.
 - These are fragile leukemic cells seen in CLL.
 - This cell is a lab artifact in which the fragile nucleus is crushed by the cover slip.



CLL: Smudge Cell

• Classification:

○ Rai Staging System:

- Stage 0 = lymphocytosis (elevated WBC)
- Stage 1 = lymphocytosis + lymphadenopathy Generalized.
- Stage 2 = lymphocytosis + hepatosplenomegaly
- Stage 3 = lymphocytosis + anemia b/c no space for RBC poiesis
- Stage 4 = lymphocytosis + thrombocytopenia

* Pathogenesis = chromosomal translocation & deletion
 L2 trisomy 12q 13q12-14 11q or 17p

Morphology = LN architecture
 - Ee diffusely effaced by small lymphocytes - round, slightly irregular nuclei -

admixed w # of larger atypical cells → prolymphocyte
 In CLL → PBF = smudge cells

○ **Binet Staging System:**

- Stage A = no anemia; no thrombocytopenia; < 3 areas of lymphoid enlargement
- Stage B = no anemia; no thrombocytopenia; ≥ 3 areas of lymphoid enlargement
- Stage C = anemia, thrombocytopenia or both; regardless of lymphoid enlargement

R_x

Treatment:

- No treatment for Rai stages 0 & 1, and Binet stage A.
- Treatment is indicated for Rai stages 2, 3, 4, and Binet stages B and C.
- Options are:
 - Purine analogues = fludarabine, penostatin
 - Alkylating agents = cyclophosphamide, chlorambucil, rituximab
 - Combination regimens are superior to monotherapy.
 - Combination regimens such as fludarabine + rituximab have increased remission rates and disease-free survival.
- Supportive Care:
 - Anemia = transfusion; Infection = antibiotic; Bleeding = platelets
 - Hypogammaglobulinemia = immunoglobulin replacement
 - Bulky disease with compressive symptoms = radiotherapy
 - Splenomegaly with refractory cytopenias = splenectomy

IV. Chronic Myelogenous Leukemia (CML):

- It is a myeloproliferative neoplasm with clonal overproduction of hematopoietic myeloid stem cells that can differentiate. *↳ of immature cells.*
- Age = 40 – 60 years.
- Gender = male predominance. *what's P.C. =>*

▪ **Genetics:**

- Philadelphia chromosome is present in 95%.
- Philadelphia chromosome involves translocation between long arm of chromosomes 9 and 22 i.e. t(9:22)
- Philadelphia chromosome involves fusion of ABL-proto-oncogene on chromosome 9 with break cluster region (BCR) on chromosome 22.
- ABL-BCR is required for the diagnosis of CML.
- Absence of Philadelphia chromosome is associated with bad prognosis.

also present
in ALL

▪ Clinical Stages:

- Chronic Phase:
 - This phase is often asymptomatic; lasting 3-5 years.
 - It may present with fatigue, weight loss, night sweats, and splenomegaly: *→ wavy*.
 - This phase is responsive to treatment and easily controlled.
- Accelerated Phase:
 - This phase is characterized by refractory leukocytosis and worsening symptoms.
 - It may present with progressive splenomegaly, bone pain, bleeding, infection, and pruritis.
 - This phase is not always seen.
- Blast Crisis:
 - **This is the most common cause of death.**
 - This phase is characterized by transformation to acute leukemia.
 - It transforms **to acute myeloid leukemia (AML)** in 70% cases; poor prognosis.
 - It transforms to acute lymphoblastic leukemia (ALL) in 30%; good prognosis.

▪ Diagnosis:

- Peripheral smear:
 - Leukocytosis ($> 100,000$)
 - Left-shifted leukocytosis i.e. with all stages of myeloid maturation.
 - Anemia, thrombocytosis, and basophilia.
 - Blood LDH and uric acid levels are elevated
- Bone Marrow:
 - Hypercellular with increased myeloid to erythroid ratio.
 - Chromosome analysis = Philadelphia chromosome
 - RNA analysis = BCR – ABL gene product
 - **Decreased leukocyte alkaline phosphatase (LAP).**
 - Myeloblasts:
 - Chronic CML = $< 10\%$
 - Accelerated CML = $10 - 20\%$
 - Blast crisis = $> 20\%$

R_x

Treatment:

- Tyrosine Kinase inhibitor – **Imatinib** (drug of choice)
- Those who fail to respond to Imatinib the options are:
 - Second-generation tyrosine kinase inhibitors (dasatinib, nilotinib)
 - Allogeneic bone marrow transplantation (especially in younger patients).
 - Classic cytotoxic drugs such as hydroxycarbamide and interferon
- Blast crisis:
 - Imatinib is indicated if the patient has not already received it.
 - When transformation occurs to acute leukemia treatment depends upon which type it is.
 - AML = poor prognosis (treatment already discussed)
 - ALL = good prognosis (treatment already discussed)

Myeloproliferative Syndromes

- It results from clonal expansion of multi-potent hematopoietic stem cell.
- It is classified into:

RBC	Polycythemia vera
WBC	Chronic myeloid leukemia (already discussed)
Platelets	Essential thrombocythemia
Fibroblasts	Myelofibrosis

I. Polycythemia Rubra Vera (PRV):

- **Definition:** it refers to increase in RBC mass with or without increase in granulocytes and platelets in the absence of physiologic stimulus.
- It is a myeloproliferative disorder characterized by clonal expansion of the myeloid stem cell i.e. increased RBCs, granulocytes, platelets, and mast cells.
- **Clinical Features:**
 - Hyperviscosity (erythrocytosis)
 - Headache, Dizziness
 - Tinnitus, Blurred vision
 - Thrombosis (Hyperviscosity; thrombocytosis):
 - Increased risk of MI, stroke, and deep venous thrombosis
 - Budd-Chiari syndrome– thrombosis of hepatic veins
 - Amaurosis fugax – transient blindness
 - Ocular migraine
 - Others:
 - Bleeding (epistaxis, easy bruising) – from abnormal platelet function
 - Pruritus after hot bath – due to increased histamine from basophils.
 - Peptic ulcer disease – due to increased histamine from basophils.
 - Gout – due to increased uric acid from cell turnover.
 - Signs:
 - Splenomegaly
 - Plethora (red face)
 - Hypertension
 - Engorged retinal veins

▪ **Lab Findings:**

- Hemoglobin > 18.5 g/dL (men), > 16.5 g/dL (women)
- Increased plasma volume (PV), (only type of polycythemia with increased PV)
- Decreased erythropoietin (EPO), (only type of polycythemia with decreased EPO).
- Oxygen saturation is normal.
- **JAK2 mutations** in 95% of cases.
- Bone Marrow:
 - Hypercellular marrow
 - Decreased iron
 - Megakaryocytic hyperplasia
 - Absence of Philadelphia chromosome

R_x

Treatment:

- Phlebotomy (Venesection):
 - Between 400 – 500 ml of blood is removed.
 - It is repeated every 5 – 7 days.
 - Target hematocrit < 45% in men, and < 42% in women.
- Low-dose aspirin (reduces risk of thrombosis)
- Hydroxyurea (if high risk of thrombosis)
- Supportive:
 - Gout = allopurinol
 - Pruritus = anti-histamines

Clinical Pearl:

Leukocyte Alkaline Phosphatase (LAP):

- LAP is increased in polycythemia Vera.
- LAP is decreased in chronic myelogenous leukemia (CML)

▪ **Types of Polycythemia:**

- Polycythemia refers to hemoglobin level greater than the upper limit of normal.
- Hemoglobin > 18.5 g/dL (men), > 16.5 g/dL (women)

Class	Mechanism	Example	Lab Findings
Primary Polycythemia	Myeloproliferative disorder	Polycythemia Vera	RBC Mass = increased PV = increased SaO ₂ = normal EPO = normal
Appropriate Secondary Polycythemia	Appropriate Polycythemia i.e. increased EPO due to tissue hypoxia	High altitude Cyanotic heart disease Lung disease	RBC Mass = increased PV = normal SaO ₂ = decreased EPO = increased
Inappropriate Secondary Polycythemia	Inappropriate Polycythemia i.e. increased EPO from ectopic site without tissue hypoxia	Renal cell carcinoma Bronchogenic carcinoma Pheochromocytoma	RBC Mass = increased PV = normal SaO ₂ = normal EPO = increased
Relative Polycythemia	It is polycythemia due to a decrease in plasma volume.	Volume depletion (vomiting, diarrhea)	RBC Mass = normal PV = decreased SaO ₂ = normal EPO = normal

PV = plasma volume, SaO₂ = saturation of oxygen, EPO = erythropoietin

II. Essential Thrombocythemia:

- Definition: increase in platelets (>450,000/ μ l) with or without increase in RBC and granulocytes.
- It is characterized by clonal proliferation of megakaryocytes leading to persistently elevated platelets, with abnormal function.
- It is the least common myeloproliferative syndrome.
- JAK 2 mutation present in 50% cases.
- Clinical features:**
 - Thrombosis and hemorrhage are the major manifestations.
 - Microvascular occlusion
 - Arterial or venous thrombosis
 - Atypical chest pain, light-headedness
 - Erythromelalgia:**
 - It refers to intense burning, pain, and erythema of extremities.
 - It is due to microvascular thrombi from platelet aggregates.
 - It can be seen in PV if platelet count is high.

▪ **Diagnosis:**

- Bone Marrow:
 - Megakaryocytic hyperplasia
 - Absence of Philadelphia chromosome
 - Lack of collagen fibrosis
 - Normal iron store
- Peripheral Smear:
 - Large hypo-granular platelets
 - Mild leukocytosis

R_x

Treatment:

- Low Risk Patients:
 - Age <40 years
 - Platelet count < 100,000/ μ l
 - No history thrombosis:
 - Aspirin
 - No need for cytoreduction
- High Risk Patients:
 - Age > 40 years
 - Platelet count > 100,000/ μ l
 - History of thrombosis
 - Aspirin, PLUS:
 - Cytoreduction with Hydroxyurea (hydroxycarbamide)

Clinical Pearl:

Thrombocytosis:

- It refers to increased number of platelets.
- **Primary thrombocytosis** refers to essential thrombocythemia.
- **Secondary thrombocytosis** is also known as **reactive thrombocytosis**.
- Secondary thrombocytosis can be due to conditions like:
 1. Inflammation = rheumatoid arthritis, inflammatory bowel disease
 2. Infection
 3. Acute bleeding
 4. Iron deficiency
 5. Post-splenectomy
 6. Hodgkin's disease

III. Primary Myelofibrosis:

- It refers to clonal myeloproliferation with reactive marrow fibrosis and extramedullary hematopoiesis.
- **Pathogenesis:**
 - It is due to JAK2 gene mutation on short arm of chromosome 9.
 - It is caused by inappropriate release of fibrogenic factors for neoplastic megakaryocytes.
 - Two important factors are:
 - Platelet-derived growth factor (PDGF)
 - Transforming growth factor-beta (TGF- β)
- **Diagnosis:**
 - Bone marrow aspirate = "dry" tap.
 - Bone marrow biopsy:
 - Severe fibrosis
 - Replacement by reticulin and collagen
 - Peripheral Smear:
 - Large abnormal platelets
 - **Leukoerythroblastic reaction:**
 - Tear-drop cells
 - Nucleated RBCs
 - Immature WBCs
- **Clinical Features:**
 - Ineffective erythropoiesis = anemia
 - Extramedullary hematopoiesis = massive splenomegaly \pm hepatomegaly
 - Portal HTN
 - Hyper-metabolic syndrome (night sweats, fever, and weight loss)
 - Splenic infarcts with left-sided pleural effusion

R_x

Treatment:

- Supportive care (anemia = transfusion, infection = antibiotics, bleeding = platelets)
- Folic acid replacement.
- Hydroxycarbamide (Hydroxyurea)
- Splenectomy
- Bone marrow transplantation

Lymphomas

- Lymphomas are neoplasms that arise from lymphoid tissues.
- Lymphoid neoplasms are classified into;
 - Hodgkin lymphoma (HL)
 - Non-Hodgkin lymphoma (NHL)

	<u>Hodgkin Lymphoma</u>	<u>Non-Hodgkin Lymphoma</u>
1	It is mostly localized to a single axial group of nodes.	It mostly involves multiple peripheral nodes.
2	Contagious spread	Non-contagious spread
3	Mesenteric nodes and Waldeyer's ring rarely involved.	Mesenteric nodes and Waldeyer's ring commonly involved
4	Extranodal involvement uncommon.	Extranodal involvement common.
5	Reed-Sternberg cells present	Reed-Sternberg cells absent.

I. Hodgkin Lymphoma:

▪ Clinical Features:

- Lymph node enlargement; most often of the cervical nodes.
 - Lymph nodes are painless with a rubbery consistency
 - Lymph nodes are involved in a "**contagious pattern**" i.e. orderly anatomic spread to adjacent nodes
- Hepatosplenomegaly
- Systemic "B" symptoms:
 - Fever
 - Drenching night sweats
 - Weight loss of > 10% bodyweight.

▪ WHO Classification:

- Classic HL:
 - Nodular sclerosis
 - Mixed cellularity
 - Lymphocyte-rich
 - Lymphocyte depletion
- Non-classic HL:
 - Lymphocyte predominance

(i). Nodular Sclerosis:

- It is the most common subtype of HL (65 – 70%).
- It is the only HL that is more common in females.
- Reed – Sternberg cells + fibrotic bands
- Epstein - Barr virus (EBV) = Negative.
- Prognosis = Excellent.

(ii). Mixed Cellularity:

- It is the second most common type (20 – 25%); more common in males.
- Reed – Sternberg cells, but NO fibrotic bands.
- EBV = positive in 70%
- Prognosis = intermediate

(iii). Lymphocyte Rich:

- It is common in old males.
- Reed-Sternberg cells + abundant normal appearing lymphocytes.
- Background infiltrates = rich in lymphocytes
- EBV = positive in 30%
- Prognosis = Good

(iv). Lymphocyte Depleted:

- It is more common in old males.
- Reed-Sternberg cells + diffuse fibrosis.
- Background infiltrate = paucity of lymphocytes
- EBV = positive (most), HIV = positive (few)
- **Prognosis = The Worst**

(V). Lymphocyte Predominant:

- It is more common young males.
- "Popcorn cells" i.e. lymphohistiocytic variant of Reed–Sternberg cells.
- EBV = negative
- **Prognosis = The Best**

▪ Staging:

Ann Arbor System

Stage I	Confined to single lymph node region
Stage II	Involvement of ≥ 2 nodal areas on the same side of diaphragm.
Stage III	Involvement of nodes on both sides of diaphragm.
Stage IV	Extranodal involvement (liver, bone marrow)

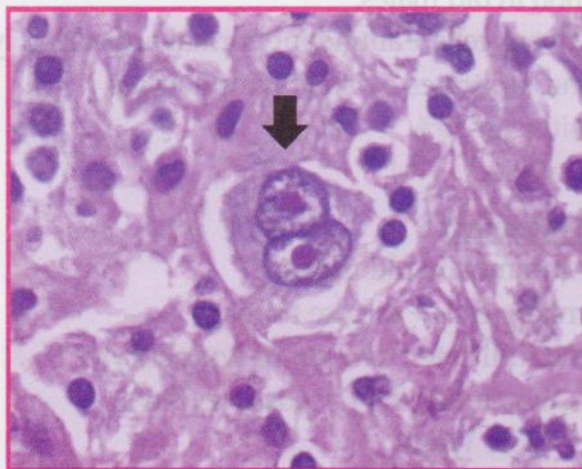
Each stage is sub-classified:

A = Absence of symptoms

B = presence of symptoms (weight loss, drenching sweats, and fever)

▪ Diagnosis:

- CBC = normal, or may show normochromic normocytic anemia, lymphopenia
- ESR = raised
- Serum LDH = raised level is associated with poor prognosis. *enzyme that is imp for energy production*
- CXR = mediastinal widening ± lung involvement
- CT scan chest, abdomen and pelvis *CAP-*
- Positron emission tomography (PET) scan – for staging and assessing response to therapy
- Excisional Lymph Node Biopsy:
 - It is the most accurate test, required for definitive diagnosis.
 - It shows characteristic "Reed – Sternberg Cells".



Reed-Sternberg Cell: Large B-cell with Bi-lobular Nuclei with halves
As mirror-images ("owl's eyes") and eosinophilic nucleoli
eosinophilic

R_x

Treatment of HL:

- Local Disease (Stage IA & IIA):
 - Chemotherapy (ABVD regimen) + Radiotherapy
- Advanced Disease (Stage III, IV, or any B-symptom):
 - Chemotherapy (**ABVD regimen**) only (6 – 8 cycles):
 - A = Adriamycin (or doxorubicin)
 - B = Bleomycin
 - V = Vincristine (or vinblastine)
 - D = Dacarbazine
- Relapse after radiotherapy = chemotherapy
- Relapse after chemotherapy = high-dose chemotherapy + bone marrow transplantation

II. Non – Hodgkin Lymphoma (NHL):

- It refers to monoclonal proliferation of lymphoid cells.
- It is of B-cell origin in 70% cases, and of T-cell origin in 30% of cases.
- **Clinical Features:**
 - Diffuse, nodal and extranodal disease, with non-contagious spread.
 - Unlike HL, NHL is widely disseminated at presentation including in extranodal sites.
 - Bone marrow involvement is more common in low-grade NHL than high-grade NHL.
 - Extranodal involvement is more common in T-cell disease than B-cell.
 - Extranodal presentation may be for example:
 - Abdominal involvement = hepatosplenomegaly
 - Skin involvement = “mycosis fungoides”
- **Diagnosis:**
 - Ann – Arbor classification is valid for NHL as well.
 - Investigations are same as that for HL.
 - No Reed–Sternberg Cells on excisional lymph node biopsy.

R_x

Treatment of NHL:

- Low-grade NHL:
 - Stage I = radiotherapy.
 - R – CVP Regimen:
 - Rituximab (anti-CD20 monoclonal antibody) +
 - Cyclophosphamide
 - Vincristine
 - Prednisolone
- High-grade NHL:
 - R – CHOP regimen:
 - Rituximab (anti-CD20 monoclonal antibody) +
 - Cyclophosphamide
 - Hydroxydaunorubicin (doxorubicin)
 - Oncovorin (Vincristine)
 - Prednisolone
 - Radiotherapy is combined with R-CHOP when:
 - Localized disease
 - Bulky disease
 - Spinal cord compression

Paraproteinemias

- Gammopathy refers to over-production of one or more classes of immunoglobulin.
- Polyclonal gammopathy means that a single clone of plasma cells produces different immunoglobulins (Ig).
- Monoclonal gammopathy means that a single clone of plasma cells produces identical immunoglobulins (Ig).
- Monoclonal immunoglobulins are called "M-proteins", or "Paraproteins".

I. Multiple Myeloma (MM):

- Introduction:
 - It is a plasma cell neoplasm (plasma cells are formed by B-cells).
 - It is the most common **symptomatic** monoclonal gammopathy.
 - Peak age is 70 years; rare under 40 years of age.
- Pathogenesis:
 - In multiple myeloma, plasma cells are monoclonal i.e. a single clone of plasma cells produces identical immunoglobulins.
 - Monoclonal immunoglobulins show "M-spike" on protein electrophoresis.
 - Most common types of monoclonal Ig or Paraproteins are:
 - IgG = 55%
 - IgA = 25%
 - Light-chain only = 22%
- Clinical Features:
 - Skeletal System:
 - Multifocal destructive (lytic) bone tumors
 - Bone pain and hypercalcemia – due to increased osteoclast activity.
 - Pathologic fractures.
 - Common site: axial skeleton:
 - Vertebral column – most common
 - Ribs; Skull; Pelvis & femur
 - Hematologic:
 - Normocytic anemia
 - Rouleaux formation due to increased serum M-proteins
 - Increased erythrocyte sedimentation rate (ESR) > 100
 - Coagulopathy and increased bleeding time.

- Renal Disease:
 - **Bence Jones Nephropathy:**
 - Bence Jones proteins refer to light-chain proteins in the urine.
 - BJ proteins cause “cast- nephropathy”, which is renal failure due to toxic effect of filtered light-chains.
 - BJ proteins damage tubular epithelium with intra-tubular multinucleated giant cell reaction.
 - Nephrocalcinosis:
 - It presents as renal failure in multiple myeloma.
 - It is metastatic calcification of tubular basement membranes in the collecting ducts.
- Amyloidosis:
 - It is AL (amyloid light-chain) type.
 - It is due to secretion of amyloidogenic Ig light chains.
 - It presents as nephrotic syndrome.
- Infections:
 - It is the **most common cause of death** in MM.
 - Recurrent infections due to decreased normal immunoglobulins.
 - Streptococcus pneumoniae, S. aureus, and E. coli are the common pathogens.
 - Cellular immunity is relatively unaffected.
- **Diagnosis:**
 - Protein Electrophoresis (PEP):
 - Serum PEP = increased Ig in serum > 3 gm/dL.
 - Urine PEP = increased BJ (light-chains) in urine (more than 6 gm/dL)
 - Increased ESR (> 100) and CRP
 - Decreased anion gap.
 - **Beta-2 Microglobulin – corresponds to disease severity (useful in prognosis)**
 - **Raised serum LDH – corresponds to disease severity (useful in prognosis)**
 - Elevated blood urea nitrogen (BUN) and creatinine
 - Elevated total protein with normal albumin.
 - Bone marrow biopsy:
 - Increased plasma cells > 10% on bone marrow biopsy.
 - **Russel bodies** (PAS positive **intra-cytoplasmic** Ig-containing inclusions)

- **Dutcher bodies** (PAS positive **intra-nuclear** Ig-containing inclusions)
- Skeletal survey = characteristic lytic lesion, mostly seen in the skull.



Clinical Pearl:

Multiple Myeloma Diagnostic Criteria:

- 2 out of 3 diagnostic features should be present:
 1. Serum and/or urinary paraprotein.
 2. Increased malignant plasma cells in the bone marrow
 3. Skeletal lytic lesions



Treatment:

- Transplant Candidates (age < 70):
 - High dose chemotherapy
 - Hematopoietic stem cell transplantation (HSCT)
- Non-transplant Candidates (age > 70):
 - Melphalan + Prednisolone, PLUS:
 - Thalidomide – OR – Lenalidomide
- Adjuvant:
 - Bone = bisphosphonates
 - Anemia = transfusion and erythropoietin
 - Infections = broad-spectrum antibiotics
 - Renal:
 - Avoid NSAIDs & IV contrast,
 - Rehydrate, and ensure adequate fluid intake
 - Dialysis may be indicated in acute renal failure

II. Monoclonal Gammopathy of Uncertain Significance (MGUS):

- It is the most common monoclonal gammopathy.
- It is characterized by small IgG M-spike in elderly patients.
- Increased risk of conversion to MM at rate of 1% per year.
- **Diagnosis:**
 - Serum monoclonal protein < 3 gm/dL.
 - No urinary BJ proteins
 - Plasma cells < 3% in bone marrow
 - No symptoms

III. Waldenstrom's Macroglobulinemia (WM):

- It is also known as "Lymphoplasmacytic Lymphoma".
- It is a B-cell neoplasm that secretes monoclonal IgM (IgM M-spike).
- **Presentation:**
 - Fatigue from anemia (most common symptom)
 - Tumor infiltration: lymphadenopathy, hepatomegaly, and splenomegaly (50% cases)
 - Hyperviscosity syndrome:
 - Blurred vision, vertigo
 - Engorged retinal veins on fundoscopy
 - Mucosal bleeding
 - Raynaud's phenomenon
 - Congestive heart failure
- **Diagnosis:**
 - Bone Marrow Biopsy:
 - Increased plasmacytoid lymphocytes.
 - Infiltration of lymphoid cells and prominent mast cells.
 - **Russel bodies** (PAS positive **intra-cytoplasmic** Ig-containing inclusions)
 - **Dutcher bodies** (PAS positive **intra-nuclear** Ig-containing inclusions)
 - Relative Serum Viscosity:
 - It is defined as ratio of viscosity of serum to water.
 - It is normally 1.8.
 - Hyperviscosity syndrome occurs when relative serum viscosity is > 5-6.

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Treatment:

- Plasmapheresis:
 - It is the best initial therapy.
 - It removes IgM and decreases viscosity.
- Long-Term:
 - Chlorambucil – OR:
 - Fludarabine and prednisone

Chapter 12

RHEUMATOLOGY



Osteoarthritis & Rheumatoid Arthritis

Osteoarthritis (OA):

I. Introduction:

- Also known as “degenerative joint disease (DJD)”.
- It is by far the most form of arthritis.
- It is defined as **chronic, non-inflammatory condition** characterized by progressive erosion of articular cartilage.
- Risk Factors:
 - Primary OA:
 - Ageing; genetic factors
 - Mechanical stress
 - Secondary OA:
 - Diabetes
 - Ochronosis (alkaptonuria)
 - Hemochromatosis
 - Marked obesity

II. Clinical Features:

- Women affected more than men.
- Weight-bearing joints are the principal joints involved:
 - Women = Knees and hands
 - Men = Hips and spine
- **Asymmetric involvement of joints.**
- Mono-articular (1 joint) or oligo-articular (1 – 4 joints)
- Larger joints are affected first.
- Onset = insidious, over months or years.
- **Morning stiffness of < 15 minutes,**
- Joint pain (most common symptom) – aggravated with movement, relieved by rest.

▪ **Signs:**

- Restriction of movements
- Palpable coarse crepitus (due to rough articular surfaces)
- Muscle weakness and wasting

III. Generalized Nodal OA & Spine OA:

▪ **Generalized Nodal OA:**

- It is OA of ≥ 1 hand interphalangeal joints.
- It has strong genetic predisposition with female predominance.
- Peak onset is in middle age (> 40 years)
- Features:
 - Pain, stiffness, & swelling of ≥ 1 PIP joints of hands.
 - Postero-lateral swellings (nodes) on each side of the extensor tendons, which harden forming osteophytes:
 - **Heberden's nodes** = prominent osteophytes at DIP.
 - **Bouchard's nodes** = prominent osteophytes at PIP.
- Symptoms are present while the node evolves and OA develops.
- Symptoms usually subside once OA is fully established, & hand function remains good.

▪ **Spine OA:**

- It predominantly affects cervical & lumbar spine.
- Cervical Spine (Cervical Spondylosis):
 - It presents with neck pain, radiating to arms.
 - Pain is aggravated with movement, relieved with rest.
- Lumbar Spine (Lumbar Spondylosis):
 - It presents with back pain, radiating to buttocks, & legs.
 - Pain is aggravated with movement \pm positive straight leg raise test.

IV. OA of Knee & Hip:

▪ **Knee OA:**

- OA targets the patella-femoral and medial tibio-femoral compartment of knee.
- Pseudogout in association with OA is most common at the knee.
- Local examination findings of knee OA may include:
 - It is usually, particularly in women, bilateral and symmetrical.
 - It can be unilateral, especially in men after trauma.
 - A jerky, asymmetric (antalgic) gait.
 - **Varus deformity** (rheumatoid arthritis causes valgus deformity)
 - Joint-line tenderness

- Weakness and wasting of the quadriceps muscle.
- Restricted flexion and extension with coarse crepitus.
- **Hip OA:**
 - Hip OA most commonly targets the superior aspect of the joint.
 - Hip shows the best correlation between symptoms and radiographic changes.
 - Hip pain is maximally deep in the anterior groin, with radiation to buttock, anterolateral thigh, knee, or shin.
 - Local examination findings of hip OA may include:
 - Antalgic gait
 - Weakness and wasting of quadriceps and gluteal muscles.
 - **Pain and restriction of internal rotation with the hip flexed – is the earliest and most sensitive sign of hip OA.**
 - Anterior groin tenderness just lateral to the femoral pulse

V. Investigations:

- CBC, ESR and CRP = normal
- Antinuclear antibody = absent
- Rheumatoid factor = absent
- X-ray of affected Joint:
 - **Asymmetrical** joint space narrowing
 - Osteophytes
 - Subchondral bone
 - Bone cysts
 - No ankylosis i.e. fusion of joints.

VI.

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Treatment:

- Non-Pharmacologic:
 - Weight loss
 - Exercise – both strengthening & aerobics
 - Quadriceps strengthening exercise – knee OA
 - Patient education
- Pharmacologic:
 - **Acetaminophen (Paracetamol) – best initial analgesic**
 - NSAIDS – both topical & oral
 - Intra-articular steroids – if other medical therapy don't control pain
 - Intra-articular hyaluronan injection – Knee OA
 - Joint replacement – if disease is severe and refractory to medical therapy.

Rheumatoid Arthritis (RA):

I. Introduction:

- It is the most common “inflammatory” arthritis.
- It is chronic, symmetric, debilitating and destructive inflammatory polyarthritis.
- It is an autoimmune disease in which unknown antigens principally attack the joints of susceptible host.
- **Pathogenesis:**
 - Both genetic and environmental factors are involved.
 - **Associated with HLA-DR4.**
 - **CD4 T-cells play a central in the pathogenesis.**
 - CD4 T-cells stimulate B-cells:
 - B-cells produce immunoglobulins, including rheumatoid factor (RF).
 - RF is an IgM autoantibody that has specificity for Fc portion of IgG.
 - CD4 T-cells also stimulate macrophages:
 - Macrophages produce inflammatory cytokines.
 - **The most important pro-inflammatory cytokines are TNF- α and IL-1, as they regulate production of other cytokines.**
 - Net Effect:
 - RF combines with IgG to produce immune complexes that activate the complement system.
 - Complement system attracts neutrophils resulting in synovitis, and eventually pannus formation.
 - **Pannus:**
 - It is granulation tissue formed within synovial tissue.
 - It is formed by fibroblasts and inflammatory cells.
 - It releases cytokines, which destroy the articular cartilage.
 - It results in ankylosis i.e. fusion of the joint by scar tissue.

II. Clinical Features:

- **Symmetric involvement of joints.**
- Polyarticular (≥ 5 joints)
- Small joints are affected first.
- Morning stiffness improves with activity.
- Constitutional symptoms (fever, fatigue, anorexia, weight loss)

Diagnostic Criteria of RA:

Diagnosis is made when ≥ 4 features are present.

1	Morning stiffness > 1 hour	5	Rheumatoid nodules
2	Arthritis of ≥ 3 joints	6	Rheumatoid factor
3	Arthritis of hand joints	7	Radiological changes (osteopenia & erosion)
4	Symmetrical arthritis	8	Duration ≥ 6 weeks

Diagnostic Criteria of RA

(European League Against Rheumatism)

(American College of Rheumatology)

<u>Joints Affected</u>		<u>Serology</u>	
1 Large Joint	0	Negative RF & CCP	0
2 – 10 Large Joints	1	Low + RF or CCP	2
1 – 3 Small Joints	2	High + RF or CCP	3
4 – 10 Small Joints	5		
<u>Duration of Symptoms</u>		<u>Acute Phase Reactants</u>	
	0	Normal CRP & ESR	0
< 6 weeks	1	Abnormal CRP & ESR	1
> 6 weeks			
Definite Diagnosis of RA = score ≥ 6			

Signs:

- Radial deviation of wrist and ulnar deviation of fingers.
- **Swan neck deformity** = PIP hyperextension, DIP flexion.
- **Boutonniere deformity** = PIP flexion, DIP hyperextension.
- **Cock-up toe deformity** = dorsal subluxation of MTP.
- Cervical joint involvement:
 - Most common site C1 – 2.
 - **ALWAYS perform cervical spine imaging before endotracheal intubation in patients with RA.**

Lab Findings:

- CBC = anemia; ESR & CRP are raised.
- Positive ANA.
- Rheumatoid Factor (RF):
 - It is positive in 70% of patients.

- Its specificity is poor, as it can be positive in other diseases & in normal population.
- High titers are associated with more severe disease & extra-articular disease.
- Anti-CCP:
 - Its sensitivity is similar to RF (70%), but higher specificity (> 95%)
 - It can become positive even before the onset of disease.
 - It is associated with more severe disease progression.
- X-ray of Hand & Wrist:
 - **Symmetrical** narrowing of joint space.
 - **Peri-articular osteopenia**
 - **Bone erosions**
 - Deformities

- ALWAYS perform cervical spine imaging before endotracheal intubation in patients with RA.
- Most common site C1 - 2.
- Cervical joint involvement
- Cock-up toe deformity = dorsal subluxation of MTP.
- Boutonniere deformity = PIP flexion, DIP hyperextension.
- Swan neck deformity = PIP hyperextension, DIP flexion.
- Radial deviation of wrist and ulnar deviation of fingers.

Lab Findings:

- CBC = anemia; ESR & CRP are raised.
- Positive ANA
- Rheumatoid Factor (RF)
- It is positive in 70% of patients.

III. Extra-Articular Manifestations:

System	Features
Cardiac	<p>Cardiac involvement occurs in up to 30% of patients with seropositive RA.</p> <p>Cardiac involvement is usually asymptomatic.</p> <p>Pericarditis, Myocarditis, Endocarditis, Conduction defects, Coronary Vasculitis, Granulomatous Aortitis:</p> <ul style="list-style-type: none"> ▪ Risk of CV disease is increased with NSAIDs & Steroids ▪ Risk of CV disease is decreased with DMARDs & biologic agents.
Pulmonary	<p>Pulmonary fibrosis (most common manifestation); Pleural effusion,</p> <p>Caplan's syndrome (RA + pneumoconiosis + lung nodules)</p>
Neurological	<p>Cervical cord compression, peripheral neuropathy, Mononeuritis multiplex</p>
Renal	<p>Glomerulonephritis; nephrotic syndrome (due to amyloidosis or as a side-effect of drugs used for treatment)</p>
Ocular	<p>"Keratoconjunctivitis Sicca" – (dry eyes) is the most common manifestation due to secondary Sjogren's syndrome.</p> <p>Episcleritis (painless), Scleritis (painful)</p> <p>"Scleromalacia" – painless bilateral thinning of sclera</p> <p>"Corneal Melting":</p> <ul style="list-style-type: none"> ▪ It occurs in long-standing disease, associated with systemic vasculitis ▪ It is devastating complication, associated with corneal thinning. ▪ If untreated, it progresses to corneal perforation. ▪ Rx – high-dose steroids & immunosuppressants
Hematologic	<p>Anemia, eosinophilia, thrombocytosis</p>
Lymphatic	<p>Felty's syndrome (i.e. RA + splenomegaly + neutropenia):</p> <ul style="list-style-type: none"> ▪ Lymphadenopathy, Skin pigmentation ▪ Normocytic normochromic anemia, & thrombocytopenia ▪ Increased risk of non-Hodgkin lymphoma.
Skin	<p>Rheumatoid Nodules:</p> <ul style="list-style-type: none"> ▪ It occurs almost exclusively in seropositive RA. ▪ It occurs at sites of pressure (extensor surfaces of forearm, Achilles tendon, toes, sacrum)



Clinical Pearl: Seropositive RA:

- It refers to RA with positive RF or **positive** anti-CCP
- It is associated with aggressive joint **disease & extra-articular** manifestations

IV.



Treatment:

▪ DMARDs:

- DMARDs = disease modifying anti-rheumatic drugs.
- **DMARDs slow the progression of disease.**
- **Methotrexate is the best initial DMARD, started along with steroids.**
- DMARDs are not useful in to relieve acute pain – takes 1 – 3 months for maximum effect.

▪ NSAIDs & Steroids:

- They are of no use in stopping the progression of disease.
- NSAIDs are the best initial therapy for the relieve of pain.
- Steroids are also used for pain relief when NSAIDs are not helping.
- Steroids are also used as a bridge when waiting for DMARDs to take effect.

Anti-Rheumatic Drugs

	Agents	Side Effects
1	<u>Methotrexate (MTX):</u> <ul style="list-style-type: none"> It is the best initial DMARD. It takes 1 – 2 months to take its effect. A 6 – month course should be given, before concluding that it has been ineffective Monitor= CBC& LFTs monthly, then every 3 mo. Supplement with folic acid (5 mg/week) 	<ol style="list-style-type: none"> Mouth ulcers Hepatotoxicity Bone marrow suppression Alopecia Pulmonary fibrosis
2	<u>Anti-Tumor Necrosis Factor (TNF) Therapy:</u> <ul style="list-style-type: none"> Agents: Etanercept, Adalimumab, Infliximab These are the first-line biologic agents for RA. These agents are often used in combination with MTX to prevent disease progression. These agents can be used as monotherapy, except for infliximab, which must be prescribed with MTX (reduces the risk of developing neutralizing antibodies) Always screen for TB (PPD and Chest x-ray) prior to starting treatment. 	<ol style="list-style-type: none"> Reactivation of latent TB Reversible lupus-like syndrome Injection site reactions Heart failure Demyelination Increased risk of malignancy (basal cell carcinoma of skin)
3	<u>Sulfasalazine</u> <ul style="list-style-type: none"> It is a DMARD used in combination with MTX & other agents. Monitor = CBC & LFTs initially monthly, then every 3 months 	<ol style="list-style-type: none"> Nausea & GI upset, Rash Hepatitis Neutropenia, Pancytopenia Orange staining (urine, contact lenses)
4	<u>Hydroxychloroquine</u> <ul style="list-style-type: none"> It is a DMARD It can be used as monotherapy in seronegative & mild disease. It is also used in combination with other DMARDs. Monitor = visual acuity & fundoscopy before starting, then annually 	<ol style="list-style-type: none"> Maculopapular rash Retinal toxicity Corneal deposits
5	<u>Penicillamine:</u> <ul style="list-style-type: none"> It is a DMARD It is less commonly used now. Monitor = CBC & Urine for protein 	<ol style="list-style-type: none"> Mouth ulcer Metallic taste Proteinuria Thrombocytopenia
6	<u>Gold:</u> <ul style="list-style-type: none"> It is a DMARD (sodium aurothiomalate) It is less commonly used now. Monitor = CBC & Urine for protein 	<ol style="list-style-type: none"> Mouth ulcer Alopecia Proteinuria Myelosuppression

Anti-Rheumatic Drugs

7 Biologic Agents:

1. **Anakinra** = IL-1 receptor antagonist
2. **Tocilizumab** = IL-6 receptor antagonist
3. **Abatacept** = CTLA4-Ig i.e. recombinant fusion protein of CTLA4 and Fc portion of IgG
4. **Rituximab** = Anti-CD20 monoclonal antibody

Never use two biologic agents concurrently in the same patient.

Juvenile Rheumatoid Arthritis (JRA):

- It refers to arthritis before the age 16 that is present for a minimum duration of 6 weeks.
- It female dominant (2:1).
- **Difference from RA:**
 - Oligoarthritis (≤ 4 joints) is more common
 - Systemic onset is more common
 - Large joints are affected more often than small joints
 - Rheumatoid nodules and RF are absent.
 - Antinuclear antibody (ANA) seropositivity is common
- **Extra-articular manifestations:**
 - High spiking-fever, often with salmon-colored rash on chest and abdomen
 - Myocarditis and pericarditis
 - Pulmonary fibrosis
 - Glomerulonephritis
 - Growth retardation and uveitis
- **Treatment:**
 - Aspirin & NSAIDs
 - Steroids for refractory cases.

	<u>Osteoarthritis</u>	<u>Rheumatoid Arthritis</u>
Nature	Non-inflammatory arthritis	Inflammatory arthritis
Pathology	Degeneration	Pannus formation
Types of joint	Large joints affected first	Small joints (esp. hand) affected first
Symmetry	Asymmetrical joint involvement	Symmetrical joint involvement
Morning stiffness	< 15 minutes	> 1 hour
Unique features	Involves distal interphalangeal joint (DIP)	Spares distal interphalangeal joint (DIP)
Lab Findings	Normal CBC, ESR, CRP	Raised ESR, CRP, + RF, anti-CCP



Clinical Pearl:

Monoarthritis:

- It involves 1 joint.
- Acute inflammatory cause = septic arthritis; gout; pseudogout.
- Chronic inflammatory monoarthritis occurs:
 - When arthritis persists for > 6 months.
 - Most common site = knee

Oligo-arthritis:

- It involves 2 – 4 joints.
- Most common cause = osteoarthritis (non-inflammatory).
- Acute inflammatory oligo-arthritis:
 - Affects lower limbs in asymmetric pattern = seronegative spondyloarthritis
 - Affects lower limbs in sequential manner (e.g. foot, then ankle, then knee) = septic arthritis

Poly-arthritis:

- It involves ≥ 5 joints.
- Most common non-inflammatory cause = osteoarthritis.
- Most common acute inflammatory cause = viral arthritis
- Most common chronic symmetrical inflammatory cause = rheumatoid arthritis.

I. Ankylosing Spondylitis (AS):

It is a seronegative spondyloarthritis.

It is a chronic inflammatory arthritis predominantly affecting sacroiliac joints and spine.

Clinical Features:

- Male dominant (3:1)
- Age = 2nd – 3rd decade
- Inflammatory back pain:
 - Low back pain due to sacroiliitis, characterized by (Mnemonic: ITAPIN):
 - Insidious onset
 - Pain at night
 - Age of onset < 40 years
 - Improves with exercise & hotwater
 - No improvement with rest
 - Morning stiffness (> 30 minutes)

Seronegative Spondyloarthritis

- It is a group of related inflammatory joint diseases distinct from rheumatoid arthritis.
- It consists of:
 - Ankylosing spondylitis
 - Reactive arthritis
 - Psoriatic arthritis
 - Arthropathy associated with inflammatory bowel disease.
- Common Features:
 - Asymmetrical inflammatory oligo-arthritis (< 4 joints)
 - Lower limb > upper limb.
 - No association with RF.
 - Enthesitis – i.e. inflammation where tendons and ligaments attach to bones.
 - Associated with HLA-B27.
- Extra-articular Manifestations:
 - Uveitis in all types.
 - Cutaneous lesions (e.g. keratoderma blenorrhagica) in reactive arthritis.
 - Nail dystrophy is psoriatic arthritis
 - Aortitis in ankylosing spondylitis.

I. Ankylosing Spondylitis (AS):

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- It is a chronic inflammatory arthritis predominantly affecting sacroiliac joints and spine.
- Clinical Features:
 - Male dominant (3: 1)
 - Age = 2nd – 3rd decade
 - Inflammatory Back Pain:
 - Low back pain due to sacroiliitis, characterized by (**Mnemonic: IPAIN**):
 - Insidious onset
 - Pain at night
 - Age of onset < 40 years
 - Improves with exercise & hotwater
 - No improvement with rest
 - Morning Stiffness (> 30 minutes)

- Flattening of normal lumbar curvature and decreased chest expansion.
 - Peripheral Arthritis:
 - It is present in up to 40% of patients with AS.
 - It is usually asymmetrical, affecting large joints, lower limb > upper limb.
 - Enthesitis:
 - It is inflammation at the site of tendon or ligament insertion into bone.
 - Sites = Achilles tendon, pre-patellar, elbow epicondyles, plantar fasciitis.
- **Extra-articular Features:**
 - Anterior uveitis (25%) – most common
 - Conjunctivitis
 - Cardiac – aortic regurgitation, mitral incompetence, AV blocks, pericarditis
 - Amyloidosis
 - Atypical upper lobe pulmonary fibrosis
 - Neurologic complications – spinal fractures, cauda equina syndrome
 - Prostatitis (80% men) – usually asymptomatic
- **Diagnosis:**
 - ESR and CRP elevated.
 - HLA-B27 positive, but is not confirmatory test.
 - X-ray of sacroiliac joint:
 - **It is the best initial test,**
 - It shows sacroiliac joint disease with erosions and sclerosis.
 - X-ray of spine:
 - **“Bamboo spine” i.e. fusion of vertebra**
 - It is due to calcification of spinal ligaments with bridging symmetric syndesmophytes.
 - MRI spine:
 - **It is the most accurate test.**
 - It detects abnormalities years before the X-ray becomes abnormal.

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Treatment:

- Patient education & physical activity – cornerstones of management:
 - Daily back extension exercises
 - **Swimming is ideal exercise.**
 - Avoidance of poor posture
- NSAIDs – best initial treatment
- Anti-TNF therapy:
 - **It is the best next therapy after NSAIDs.**
 - Agents: etanercept, infliximab, adalimumab
 - It is used when there is persistent active inflammation.
 - It produces rapid, dramatic, and sustained reduction of symptoms and of spinal and peripheral arthritis.
- DMARDs (Methotrexate):
 - It is useful for peripheral arthritis, uveitis, & extra-articular manifestations.
 - It has no effect on spinal disease as well as enthesitis.

II. Reactive Arthritis:

- It is a Seronegative Spondyloarthritis.
- It is predominantly a disease of young men with a sex ratio of 15: 1.
- It is the most common cause of inflammatory arthritis in men aged 16 – 35 years.
- **Clinical Features:**
 - Acute onset, asymmetrical arthritis affecting lower limbs > upper limbs.
 - Arthritis occurs a few days to a couple of weeks after infection:
 - Sexually transmitted infection – Chlamydia, Ureaplasma urealyticum
 - Gastrointestinal infections – Shigella, Salmonella, Campylobacter, Yersinia
 - The first attack of arthritis is self-limiting, with spontaneous remission within 2-4 months
 - However, recurrent arthritis develops in 60% of patients.
 - Associated with:
 - Low back pain & stiffness
 - Sacroiliitis – 15 – 20% patients
 - **Reiter's syndrome:**
 - Reactive arthritis
 - Non-gonococcal urethritis
 - Conjunctivitis

▪ **Extra-articular Features:**

- Nail dystrophy with subungual hyperkeratosis.
- Painless mouth ulcers – tongue, palate, buccal mucosa, lips
- Uveitis:
 - It is rare with the first attack.
 - It, however, occurs in 30% of patients with recurring arthritis.
- Cutaneous Lesions:
 - **"Circinate Balanitis"** – painless superficial ulceration of glans penis.
 - **"Keratoderma Blenorrhagica"** – painless, large crusty plaques and pustules of feet, palms, trunk, scalp, and scrotum.

▪ **Diagnosis:**

- Raised ESR and CRP
- Synovial fluid examination:
 - Inflammatory cells
 - Giant macrophages (Reiter's cells)
- X-ray:
 - Early = soft tissue swelling and effusions around affected joints
 - Late = asymmetric proliferation of bone at site of inflammation
 - Asymmetric and unilateral sacroiliitis (unlike AS, which is symmetric)
- PCR of urine or genital swab for Chlamydia
- Stool cultures

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Treatment:

- Acute Attack:
 - Rest
 - NSAIDs & analgesics
 - Intra-articular steroids – patients with severe synovitis
 - Antibiotics – if evidence of active or antecedent infection.
 - Anterior uveitis:
 - It is a medical emergency.
 - It is treated with corticosteroids – topical, systemic, or subconjunctival.
- DMARDs are indicated:
 - Persistent marked symptoms
 - Recurrent arthritis
 - Severe keratoderma blenorrhagica



Clinical Pearl:

Radiographic Appearance of Sacroiliitis:

- X-ray appearance of sacroiliitis in ankylosing spondylitis:
 - Bridging syndesmophytes are marginal.
 - Bridging syndesmophytes are fine and symmetrical.
- X-ray appearance of sacroiliitis in reactive arthritis:
 - Bridging syndesmophytes are non-marginal.
 - Bridging syndesmophytes are coarse and asymmetrical.

III. Psoriatic Arthritis (PsA):

- It is a Seronegative Spondyloarthritis.
- It is seen in 7% of patients with psoriasis, & may precede the onset of skin disease.
- Age 25 – 40 years.
- Clinical Features:
 - Asymmetrical Inflammatory Oligoarthritis:
 - **It is the most common presentation;** seen in 40% of patients.
 - DIP joint arthritis is the most typical pattern of joint involvement in psoriasis.
 - **"Sausage digits"** from enthesitis.
 - Symmetrical Polyarthritis:
 - It occurs in 25% of cases.
 - It predominates in women and resembles rheumatoid arthritis.
 - Nodules, & extraarticular features of RA are absent, and is less severe.
 - Psoriatic Spondylitis
 - It presents clinically similar to AS, but less severe.
 - It is typically unilateral & asymmetric in severity.
 - Arthritis Mutilans:
 - It is a severe, deforming erosive arthritis; occurs in 5% of cases.
 - It causes marked cartilage, bone destruction & shortening (**telescopic fingers**).
 - Extra-articular features:
 - Nail Changes:
 - It occurs in 30% of patients with psoriasis.
 - It occurs in 85% of patients with psoriatic arthritis:
 - Pitting; Onycholysis
 - Subungual hyperkeratosis; Horizontal ridging

▪ **Diagnosis & Management:**

- X-ray:
 - “Pencil – in – Cup” deformity at DIP.
 - Spinal involvement; sacroiliitis
- Treatment:
 - NSAIDs and intra-articular steroids for symptom control
 - DMARDs – methotrexate is the treatment of first choice.
 - Anti-TNF therapy – when response to DMARDs is inadequate
 - Ustekinumab:
 - It is biologic agent, targeting interleukin IL-12/23 receptor.
 - It is highly effective for psoriatic skin disease & is often effective in PsA.
 - PUVA therapy:
 - It is photo-chemotherapy using psoralen + UVA (ultraviolet A).
 - It is used for skin disease, but can be helpful for synchronous PsA.

IV. Enteropathic Arthritis:

- It refers to arthritis occurring in association with inflammatory bowel disease (IBD).
- It occurs in 10% of patients with ulcerative colitis and 20% of patients with Crohn’s disease.
- **Clinical Features:**
 - Acute inflammatory Oligoarthritis
 - Arthritis is peripheral, migratory, asymmetric, and non-deforming.
 - **Course of arthritis coincides with exacerbation of gastrointestinal disease.**
 - Spondylitis – course doesn’t coincide with gastrointestinal disease.
 - Sacroiliitis.
 - Extra-articular manifestations:
 - “Erythema nodosum” – red, tender nodules due to panniculitis
 - “Pyoderma Gangrenosum” – neutrophilic dermatosis with painful ulcers and violaceous border.
- **Treatment:**
 - Arthritis often remits with treatment of bowel disease.
 - **Arthritis can be cured by total colectomy in patients with ulcerative colitis.**
 - DMARDs & biologics are occasionally required.

Crystal Deposition Arthritis

Gout:

I. Introduction:

- It is a type of crystal-deposition disease, characterized by deposition of "monosodium urate" (MSU) crystals into the joints and other tissues.
- It is the most common inflammatory arthritis in men.
- **Causes:**
 - Primary Gout: (90% cases)
 - Metabolic defect is uric acid overproduction.
 - In 90% of cases primary gout is idiopathic.
 - In 10% of cases it is caused by enzyme deficiencies – PARTIAL hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency.
 - Secondary Gout: (10% cases)
 - Uric Acid Overproduction:
 - Myeloproliferative disorders; alcoholism
 - **Lesch-Nyhan syndrome** (complete HGPRT deficiency)
 - Uric Acid Under-excretion:
 - Dehydration; decreased renal function
 - Drugs: diuretics, pyrazinamide, salicylates, ethambutol
- **Risk Factors:**
 - Aging (after 30 years)
 - Male dominant (male: female is > 5: 1)
 - Obesity (metabolic syndrome)
 - Heavy alcohol consumption (predominantly beer)
 - Diet high in red meat and fructose
 - Diet low in vitamin C or coffee
 - **"Saturnine gout"** – lead poisoning
 - Hyper-uricemia:
 - Plasma urate level >7gm/dL is considered elevated.
 - Hyper-uricemia is defined as serum uric acid level > 2 standard deviations above mean for the population.

II. Clinical Course:

- **Acute Gout:**
 - It presents as sudden onset of monoarticular arthritis, lower limb > upper limb.
 - It typically involves the first metatarsophalangeal (MTP) joint ("**podagra**") 50%.

- It is characterized by excruciating pain, localized warmth, tenderness, and leukocytosis.
- It can occasionally be polyarticular – especially in subsequent attacks.
- Precipitants of Acute Attack:
 - Sudden change in UA levels
 - Increased dietary purine
 - Surgery, infection, dehydration
 - Medications (diuretics, urate lowering agents)
- **Chronic Gout:**
 - It is characterized by formation of **“tophi”** in soft tissue around joints.
 - **Tophi are pathognomonic hallmark of gout.**
 - Tophi are large aggregations of urate crystals surrounded granulomatous reaction with foreign body giant cells.
 - Sites – joints (fingers, wrists, knees), Achilles tendon, pinna
 - Tophi destroy subjacent bone causing erosive arthritis and severe crippling disease.
 - On average, it takes about 12 years between initial episode of acute attack and development of chronic gout.
- **Complications:**
 - Hypertension
 - Coronary heart disease
 - Kidney:
 - Uric acid stones
 - Urate nephropathy (interstitial deposits)

III. Diagnosis:

- Uric acid level doesn't help in diagnosis (it may be normal in acute attack).
- Acute attack = elevated ESR, WBC count.
- Arthrocentesis (Joint aspiration):
 - **It is the most accurate test**
 - It shows MSU crystals
 - WBC count = 20,000 – 100,000/mm³
 - Polarized microscopy shows:
 - **Crystals are needle-like**
 - **Negatively birefringent**

(Always check for Gram stain & culture of joint aspiration, because infection can coexist with gout)

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Management:

▪ Acute Attack:

- NSAIDs:
 - **It is the standard treatment – best initial therapy.**
 - Side effects: gastritis; decrease dose in renal insufficiency
- Colchicine:
 - It is used as an alternative to NSAIDs, given orally.
 - Inhibits microtubule assembly in neutrophils, preventing chemotaxis & phagocytosis.
 - Side effects:
 - Nausea, vomiting, diarrhea
 - IV form associated with bone marrow suppression, myelopathy
 - Decrease dose in renal failure (however, not nephrotoxic)
- Steroids:
 - Short course of steroids is highly effective in acute attacks.
 - **However, rule out infection first before starting steroids.**
 - Route:
 - If ≤ 2 joints involved = intra-articular
 - If > 2 joints involved = systemic (oral, IV)
 - Indications:
 - When no response to NSAIDs.
 - Contraindications to NSAIDs such as renal insufficiency.

▪ Chronic Management:

- Avoid high-purine diet (meat, seafood)
- Avoid alcohol consumption
- Avoid hyperuricemia promoting drugs (e.g. thiazide diuretics)
- Urate Lowering Therapy:
 - **Target serum uric acid level < 360 μmol/L (< 6 mg/dL)**
 - Indications:
 - Recurrent attacks of acute gout (≥ 1 acute attack/year)
 - Tophi (≥ 1)
 - Nephrolithiasis
 - Evidence of bone or joint damage
- Allopurinol:
 - **It is the drug of choice in urate lowering therapy.**

- Mechanism = xanthine oxidase inhibitor; decreases uric acid synthesis
- It is basically used in uric acid over-producers (urine uric acid > 600 mg/24hr)
- It should never be used within a month of acute attack.
- **It can precipitate an acute attack.**
- **However, once started the patient must continue it, even if an attack occurs.**
- To prevent an acute attack it is advisable to start it under cover of NSAIDs or colchicine for first 2-4 weeks before and 4 weeks after initiating therapy.
- Side effects
 - Skin rash and GI upset (most common).
 - Hypersensitivity reaction (most serious adverse effect)
 - Renal failure; bone marrow suppression, hepatitis

○ **Febuxostat:**

- It is a non-purine xanthine oxidase inhibitor.
- It is used if there is allopurinol intolerance or failure or chronic kidney disease.
- Side effects = liver toxicity, rash, arthralgia

○ **Uricosuric Agents (Probenecid & Sulfinpyrazone):**

- These agents increase urinary excretion of uric acid.
- These can be used for under-excretors of uric acid (urine UA < 600 mg/24hr).
- Contraindications:
 - Uric acid over-producers
 - Renal impairment
 - Urolithiasis

○ **Pegloticase:**

- It is a biologic agent, given intravenously.
- Indicated for treatment of tophaceous gout resistant to standard therapy.
- It is highly effective at controlling hyperuricemia & regression of tophi.
- Side Effects:
 - Infusion reactions – managed with anti-histamines & steroids
 - Acute attack – during first 3 months of therapy
 - Antibodies to pegloticase – limits long-term use of drug



Clinical Pearl: Recurrent Gout:

- In order to decrease the risk of acute attacks in patients with chronic gout, start Urate lowering therapy (indications above) + Pharmacologic Prophylaxis.
- Pharmacologic Prophylaxis:
 - It should be continued for ≥ 6 months if recurrent
 - **Low-dose Colchicine** – agent of choice (50% reduction of flares)
 - NSAIDs – less effective
 - Low-dose steroid (<10 mg/day) – least effective

Calcium Pyrophosphate Dihydrate (CPPD) Deposition Disease:

I. Introduction:

- It is a crystal-deposition disease, characterized by deposition of CPPD crystals within tendons, ligaments, articular capsules, synovium, and cartilage.
- Etiologies:
 - Idiopathic
 - Metabolic (3 H's):
 - Hemochromatosis
 - Hyperparathyroidism
 - Hypomagnesemia
 - Joint trauma
 - Familial chondrocalcinosis – autosomal dominant disorder
 - Diabetes
 - Wilson's disease

II. Clinical Features:

- **Chondrocalcinosis:**
 - It refers to calcification of cartilage, resulting from CPPD deposition.
 - It is usually asymptomatic, found incidentally on X-ray examination.
 - Incidence increases with age (rare under the age of 55).
 - Symptomatic disease can take any of the following forms:
- **Pseudogout:**
 - It is an acute inflammatory arthropathy that resembles acute gout.
 - Sites – knee (most common site), ankle, wrists
 - The affected joint is warm, tender, red, with signs of a large effusion.
 - Fever is commonly present.
 - Precipitants – surgery, trauma, severe illness

▪ **Pyrophosphate Arthropathy:**

- It is chronic arthropathy affecting same joints as Pseudogout.
- It resembles osteoarthritis, characterized by chronic pain, and morning stiffness.
- "Pseudo – Rheumatoid Arthritis:
 - It can also resemble features of RA, however, unlike RA:
 - Tenosynovitis & extra-articular features are absent
 - Affects large & medium rather than small joints.

III. Diagnosis:

- Pseudogout is indistinguishable from gout except through synovial fluid analysis.
- Arthrocentesis:
 - It is the most accurate test, distinguishing it from gout.
 - WBC 20,000 – 100,000/mm³
 - Polarized microscopy shows:
 - **Crystals are rhomboid-shaped**
 - **Positively birefringent**
- Radiographs:
 - X-ray of the affect joint shows chondrocalcinosis.
 - However, absence of calcification does not exclude the diagnosis.
- Screening:
 - Screening for secondary causes should undertake in patients:
 - Who are < 25 years old
 - Who have severe disease – polyarticular disease
 - Screening for secondary causes:
 - Serum Ca, Mg, Iron, Ferritin, TIBC
 - Urinalysis, PTH

IV. Treatment:

- Joint aspiration provides symptomatic relief.
- NSAIDs – best initial therapy
- Intra-articular steroids – if no response to NSAIDs
- Colchicine – prevents subsequent attacks.

Infectious Arthritis

Septic Arthritis:

I. Introduction:

- It is an infection of any kind that finds its way into the joint space.
- **It is a medical emergency;** with a mortality of 10%.
- It is the most rapid and destructive joint disease.
- It is relatively rare in an undamaged joint.
- Risk Factors:
 - Immunocompromised host (diabetics, HIV, elderly)
 - Damaged joints – RA, OA, gout, trauma,
 - Bacterial seeding:
 - Hematogenous spread (most common) - either skin or upper respiratory tract.
 - Direct inoculation or spread from contagious focus (e.g. cellulitis)

II. Clinical Features:

- Acute onset of mono-articular arthritis with pain, swelling, and warmth.
- Constitutional symptoms: fever, chills, sweats, malaise, myalgia, pain
- Common sites:
 - Knee (most common)
 - Hip
 - Wrist, shoulder
 - Ankes
- Agents:
 - Staphylococcus aureus (most common)
 - Streptococcus
 - Gram negative rods
 - Gonococcal (N. gonorrhoeae) – sexually active young adults

III. Diagnosis:

- Leukocytosis
- Raised ESR, and CRP – can used to monitor response to treatment
- Arthrocentesis (Joint fluid Aspiration)
 - **It is the best initial and the most accurate test.**
 - It shows:
 - WBC > 50,000 cells.
 - > 90% polymorphs (neutrophils)
 - Gram stain positive in 50% cases

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- Culture positive in 90% of cases.
- Gonococcal Infection:
 - Gram stain positive in 30% cases only.
 - Therefore, obtain concurrent genital tract cultures (positive in 70 – 90%)

Treatment:

- Prompt empiric antibiotics
- Duration of Treatment:
 - Intravenous antibiotics should be continued for at least 2.
 - Then switch to oral antibiotics for 4 weeks (total duration of 6 weeks)
- **Adult (Relatively Healthy):**
 - Flucloxacillin (2g IV 6-hourly) is the antibiotic of first choice.
 - It will cover most staphylococcal and streptococcal infections.
 - Alternatives:
 - First-generation cephalosporin – IV cefazolin – OR –
 - IV vancomycin
- **Suspected Gram-negative Arthritis:**
 - Patient Population:
 - Elderly
 - Immunocompromised
 - Gastrointestinal infection
 - IV drug users
 - Add:
 - Third generation cephalosporin – IV Ceftriaxone, IV Ceftazidime – OR
 - Aminoglycoside – IV gentamicin
 - Suspected Pseudomonas:
 - Aminoglycoside (amikacin), PLUS:
 - Anti-pseudomonal penicillin – Piperacillin – Tazobactam
- **Suspected Gonococcal Arthritis:**
 - Patient Population – sexually active young adults
 - Regimen – third-generation cephalosporin (IV ceftriaxone, IV Cefotaxime)

Analysis of Joint Fluid				
Test	Normal	Non-inflammatory	Inflammatory	Septic
Appearance	Clear	Clear; yellow	Clear to opaque	Opaque
WBC/mm ³	< 200	< 2000	> 2000	> 2000; usually > 50,000
Neutrophils	< 25%	< 25%	≥ 50%	≥ 75%
Culture	Negative	Negative	Negative	Positive
Conditions		Osteoarthritis	RA, seronegative spondyloarthritis, crystal deposition	Infection

Osteomyelitis:

I. Introduction:

- It refers to infection & inflammation of bone and marrow.
- **Routes:**
 - Hematogenous
 - It is the most common route.
 - Example: *S. aureus*, Mycobacterial infection of vertebral body (Pott's disease)
 - Contiguous Focus:
 - Traumatic (open) fracture – *S. aureus*, *S. epidermidis*
 - Orthopedic surgery – *S. aureus*, *S. epidermidis*
 - Skin breakdown + Vascular insufficiency (diabetic foot) – Polymicrobial
- **Organisms:**
 - Most common agent = *S. aureus* (80 – 90%)
 - Intravenous drug users = *S. aureus*
 - Neonates = *Hemophilus influenza*
 - Sickle cell disease = *Salmonella*
 - Foot puncture wound = *Pseudomonas aeruginosa*
 - Diabetic foot = Polymicrobial (aerobic + anaerobic)
 - Hip replacement = *Staphylococcus epidermidis*.
 - No organism = 50% cases.
- **Morphology:**
 - Most common site = metaphysis of long bones.
 - Bone necrosis due to suppurative inflammation and vascular insufficiency
 - **Sequestrum** i.e. dead piece of bone
 - **Involucrum** i.e. new bone formation

II. Clinical Features & Treatment:▪ **Clinical course:**

- Localized bone pain, tenderness,
- Warmth, swelling, erythema, and limited motion of the adjacent joint.
- Fever, malaise, and chills
- Leukocytosis
- ESR:
 - ESR > 70 greatly increases the likelihood of osteomyelitis
 - **ESR is also used to follow response to therapy.**
- X-ray:
 - It is normal in early course of disease.
 - Lytic lesions with surrounding sclerosis – seen after 2 – 6 weeks
- MRI:
 - It can detect very early changes.
 - It is performed when X-ray is normal.
- Bone Scan is performed only when MRI is contraindicated – (pacemaker)
- CT can demonstrate periosteal reaction, but is not very helpful.
- Biopsy (Culture from Tissue):
 - **It is the most accurate test.**
 - NEVER culture the drainage, or take swabs of ulcers (cannot distinguish superficial colonization from infective agent)

▪ **Treatment:**

- Surgical debridement of necrotic infected bone.
- IV antibiotics for 4 – 6 weeks – based on culture & sensitivity.

Connective Tissue Diseases

Systemic Lupus Erythematosus (SLE):

I. Introduction:

- Definition: it is a multisystem inflammatory autoimmune disease with a broad spectrum of clinical manifestations in association with antinuclear antibody (ANA) production.
- Epidemiology:
 - It is the most common connective tissue disease.
 - In 90% of cases, the affected individuals are women.
 - Age = 20 – 30 years
 - Compared to normal population, patients with lupus have a fivefold increased mortality.
- Pathogenesis:
 - Both genetic and environmental factors are involved.
 - Genetic links appear to be located on chromosome 6.
 - The characteristic feature of SLE is production of auto-antibodies.
 - Many of the target auto-antigens are intracellular and intra-nuclear components.
 - It is likely that the wide spectrum of autoantibody production results from polyclonal B and T-cell activation.
 - Environmental Factors:
 - Epstein – Barr virus
 - Ultraviolet light
 - Estrogen
 - Drugs (e.g. hydralazine)

II. Clinical Features:

- Musculoskeletal Features:
 - Joint involvement is the most common clinical feature (> 90%)
 - Like RA it causes symmetrical arthritis involving small joints.
 - Unlike RA, it causes joint pain without deformation (**i.e. non-erosive arthritis**). That is why x-ray is normal.
 - Raynaud's phenomenon + arthritis are one of the most common presentations of SLE.
 - Jaccoud's Arthropathy:
 - It is a rare manifestation of SLE.
 - In this case SLE causes major joint deformity resembling RA.

- **Cutaneous Manifestations:**
 - Photosensitivity
 - Oral ulcers
 - Malar rash (20%):
 - It is a classic butterfly facial rash with sparing of nasolabial folds.
 - It is erythematous, raised, and painful precipitated by UV light.
 - Discoid rash:
 - It appears on the face as well-defined erythematous plaques.
 - It is characterized by hyperkeratosis and follicular plugging.
 - It may cause scarring alopecia if present on the scalp.
- **Cardiopulmonary Manifestations:**
 - Cardiac Features:
 - Pericarditis (most common)
 - Myocarditis; Libmann-Sacks endocarditis
 - Pulmonary Features:
 - Recurrent pleurisy & pleural effusion (most common)
 - Shrinking lung syndrome; Pneumonitis
- **Neurologic & Hematologic:**
 - Neurologic:
 - Seizures or psychosis; Epilepsy; migraines
 - Cranial and peripheral neuropathies; Stroke
 - Hematologic:
 - Hemolytic anemia; leukopenia
 - Lymphopenia; thrombocytopenia
- **Renal Manifestations:**
 - It is one of the main determinants of prognosis.
 - The typical renal lesion is a proliferative glomerulonephritis.
 - Proteinuria; RBC casts.
 - WHO-Classification of Lupus Nephritis:

▪ Class I	= Minimal mesangial glomerulonephritis
▪ Class II	= Mesangial proliferative glomerulonephritis
▪ Class III	= Focal proliferative glomerulonephritis
▪ Class IV	= Diffuse proliferative glomerulonephritis
▪ Class V	= Membranous glomerulonephritis
▪ Class VI	= Advanced sclerotic glomerulonephritis

III. Diagnosis:

- CBC = leukopenia, lymphopenia, thrombocytopenia
- ESR = elevated; but CRP is usually normal.

- Urea and creatinine & urinalysis = proteinuria, cellular casts,
- Decreased complement levels (C3, C4):
 - They can correlate with disease activity.
 - They can drop further with acute disease exacerbations.
- Autoantibodies:
 - **Anti – Neutrophilic Antibody (ANA):**
 - It is the best screening test (high sensitivity).
 - If negative, it is unlikely that the patient has SLE.
 - **Anti-double stranded DNA (anti-dsDNA) Antibody:**
 - It is highly specific for SLE (>95%).
 - Its sensitivity is poor (30%).
 - It can be used in disease monitoring.
 - High titers are associated with:
 - Severe disease, High risk of relapse
 - Renal involvement, CNS involvement
 - **Anti-Smith (Anti-Sm) Antibodies:**
 - It is highly specific for SLE..
 - It is associated with renal disease.



Clinical Pearl: **SLE & Antibodies:**

- Anti – phospholipid Antibodies
- Anti – ribonucleoprotein antibody (anti – RNP)
- Anti – La antibody (anti-SS-B) = SLE (20-60%), also found in Sjogren's syndrome
- Anti – Ro antibody (anti-SS-A) = SLE (35-60%), also found in Sjogren's syndrome
 - It is associated with photosensitivity and thrombocytopenia
 - Maternal anti-Ro antibodies are associated with:
 - Neonatal lupus
 - Congenital heart block

Diagnostic Criteria for SLE

Diagnosis = presence of ≥ 4 of following 11 criteria

Not all 4 Criteria Must be Present at a Given Time

- Cutaneous:
 1. **Malar rash**
 2. **Discoid rash**
 3. **Photosensitivity**
 4. **Oral ulcers, Nasopharyngeal Ulcers**
- Musculoskeletal:
 5. **Non – erosive Arthritis**
- Cardiopulmonary:
 6. **Serositis** (pleuritis, pleural effusion, pericarditis, pericardial effusion)
- Renal:
 7. **Proteinuria** (> 500 mg/dL, 3+ on dipstick) – OR
RBC Casts
- Neurologic:
 8. **Seizures** –without other cause – OR
Psychosis – without other cause
- Hematologic:
 9. **Hemolytic Anemia** – OR
Leucopenia ($< 4000/\text{mm}^3$) – OR
Lymphopenia ($< 1500/\text{mm}^3$) – OR
Thrombocytopenia ($< 100,000/\text{mm}^3$)
- Serologies (Immunologic):
 10. **Positive ANA**
 11. **Positive Anti-dsDNA, Anti-Sm, or Anti-phospholipid Antibodies**

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Treatment:

- Avoid sun-exposure.
- Analgesics and NSAIDs for mild disease limited to skin & joints.
- Hydroxychloroquine is used for moderate skin and joint symptoms.
- Belimumab:
 - It is used in patients with arthritis, Serositis, or skin disease.
 - Its efficacy is increased in patients with positive anti-dsDNA or decreased C3, C4.
- Acute Flares:
 - High-dose IV steroids (1mg/kg)+ IV cyclophosphamide
 - Indicated in acute flares, renal, CNS, & cardiac involvement.
 - High-dose steroids + Mycophenolate is an alternative regimen for lupus nephritis.
- Maintenance Therapy:
 - Oral Steroids, PLUS:
 - Immunosuppressants:
 - Azathioprine (2 mg/kg/day),
 - Methotrexate (10 – 25 mg/wk),
 - Mycophenolate (2 – 3 g/day)
- Renal Disease:

Class	Presentation	Treatment
Class – I	Normal UA & creatinine	No specific treatment
Class – II	Micro-hematuria, Proteinuria	No specific treatment ± ACE – inhibitors
Class – III	Hematuria, Proteinuria, HTN,	Induction with steroids + mycophenolate or cyclophosphamide
Class – IV	Decreased GFR, ± Nephrotic syndrome	Maintenance with mycophenolate or azathioprine
Class – V	Proteinuria, Nephrotic syndrome	ACE – inhibitors If nephrotic range proteinuria – same treatment as for III & IV
Class – VI	ESRD	Renal replacement therapy

All stages benefit from Hydroxychloroquine



Clinical Pearl:

Cyclophosphamide:

- It can cause hemorrhagic cystitis.
- It can be prevented by using "**mesna**", which binds its urotoxic metabolites.
- It can also cause permanent azoospermia & anovulation.
- Consider sperm or ova collection & storage prior to starting this drug.

V. Drug-Induced Lupus:

- There are drugs that can cause lupus-like syndrome e.g.:
 - Hydralazine; Isoniazid; Procainamide
 - Penicillamine; Methyldopa; Quinidine
 - Anti-TNF (e.g. infliximab)
 - Interferons
- Difference from SLE:
 - It is generally milder disease with predominantly arthritis and Serositis.
 - It is usually **reversible** within 4 – 6 weeks after stopping medications.
 - Labs:
 - **Anti – histone antibodies = positive**
 - Anti – dsDNA = negative
 - Anti – Sm = negative
 - Complement levels = normal

Systemic Sclerosis:

I. Introduction:

- It is a generalized disorder of connective tissue affecting skin, internal organs and vasculature.
- Definitions:
 - Scleroderma = presence of tight, thickened skin
 - Systemic sclerosis = scleroderma + internal organ involvement
- Pathogenesis:
 - The cause of systemic sclerosis is poorly understood.
 - There is evidence for a genetic component.
 - Immunologic Dysfunction:
 - T-cells infiltrate the skin, and there is abnormal fibroblast activation.
 - This leads to increased production of extracellular matrix in the dermis, primarily type-I collagen.
 - This results in sclerodactyly – thickening, tightening, & induration of skin.
 - Arterial narrowing due to intimal proliferation & vessel wall inflammation.

- Endothelial injury results in release of vasoconstrictors & platelet activation.
- This results in ischemia, which exacerbates the fibrotic process.

II. Clinical Features:

Skin Involvement:

- Tightening and thickening of extremities, face, trunk.
- Puffy hands, carpal tunnel syndrome, sclerodactyly
- Immobile, pinched, "mouse-like" facies and "purse-string" mouth.
- Calcinosis cutis (subcutaneous calcifications)
- Telangiectasias
- Raynaud's phenomenon

Gastrointestinal Involvement:

- Gastroesophageal reflux disease (GERD) and erosive esophagitis
- Esophageal dysmotility = dysphagia, odynophagia, aspiration
- Gastric dysmotility = early satiety and gastric outlet obstruction
- Small bowel dysmotility = bloating, diarrhea, Malabsorption.

Cardiopulmonary Involvement:

- Pulmonary involvement:
 - It is a major (# 1) cause of morbidity and mortality.
 - Pulmonary fibrosis typically develops within 4 years.
 - Pulmonary hypertension typically develops after many years..
- Cardiac Involvement:
 - Myocardial fibrosis, Pericardial effusion
 - Conduction defects

Renal Involvement:

- It presents as hypertensive renal crisis – "**Scleroderma Renal Crisis**".
- It manifests as acute onset malignant HTN + renal failure.
- It is more common in DCSS than in LCSS.
- It is associated with poor prognosis with 50% mortality.

Endocrine Involvement:

- Amenorrhea & infertility
- Thyroid fibrosis ± hypothyroidism

III. Types:

Limited Cutaneous Systemic Sclerosis (LCSS):

- It is present in 70% of cases.
- Skin = thickening on extremities "DISTAL" to elbows & knees, and face only.
- **Pulmonary hypertension > pulmonary fibrosis**

- Renal crisis – less common & later in disease course
- Prognosis = good (>70% survival at 10 years)
- Anti-centromere antibodies (60%), ANA positive (70%)
- CREST syndrome i.e.
 - Calcinosis
 - Raynaud's phenomenon
 - Esophageal dysmotility
 - Sclerodactyly
 - Telangiectasias

▪ **Diffuse Cutaneous Systemic Sclerosis (DCSS):**

- It is present in 30% of cases.
- Skin = thickening on distal & "PROXIMAL" extremities, face, and trunk.
- Pulmonary fibrosis > pulmonary HTN.
- Renal crisis – more common & early in disease course
- Prognosis = poor (40 - 60% survival at 10 years)
- Anti-topoisomerase (Scl-70) antibodies (30%); ANA positive (70%)
- Raynaud's phenomenon

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Treatment:

- Pericarditis = NSAIDs or steroids
- Arthritis = acetaminophen, NSAIDs, hydroxychloroquine
- Raynaud's phenomenon:
 - Avoid cold exposure; warm clothes
 - Calcium channel antagonists
 - Intermittent infusions of prostacyclin –benefits severe digital ischemia
 - Bosentan (endothelin – 1 antagonist) – healing of digital ulcers
- Pulmonary:
 - Pulmonary fibrosis = cyclophosphamide
 - Pulmonary HTN = pulmonary vasodilators:
 - Bosentan (endothelin-1 antagonist)
 - Nitric oxide; prostacyclin
- Renal:
 - Monitor blood pressure monthly.
 - ACE-inhibitors for HTN crisis.
- Gastrointestinal:
 - GERD = proton pump inhibitors (PPIs)
 - Malabsorption (bacterial overgrowth syndrome) = antibiotics
 - Hypomotility = metoclopramide, erythromycin

Mixed Connective Tissue Disease (MCTD)

I. Introduction:

- It is a condition that has features of SLE, systemic sclerosis, and polymyositis.
- Clinical Features:
 - Raynaud's phenomenon – most common
 - Hands edema; sclerodactyly
 - RA-like arthritis without erosions
 - Pulmonary HTN and fibrosis
 - GI dysmotility
 - Renal HTN crisis or glomerulonephritis:
 - Low risk in MCTD
 - If either present, reconsider diagnosis of MCTD.

II. Management:

- Diagnosis:
 - ANA positive, RF positive (50%)
 - **Anti-ribonucleoprotein (anti – RNP)**
 - It is present by definition in MCTD.
 - But is not specific, also seen in SLE.
- Treatment focuses on treating the individual components of the syndrome.

Sjogren's syndrome:

I. Introduction:

- It is an autoimmune disorder characterized by chronic dysfunction of exocrine glands (salivary and lacrimal glands) due to lymphoplasmacytic infiltration.
- Causes:
 - Primary (idiopathic)
 - Secondary i.e. associated with:
 - Rheumatoid arthritis
 - SLE
 - Scleroderma; polymyositis
 - Hypothyroidism; HIV

II. Clinical Features:

- Age of onset 40 – 60 years.
- Female > male (9: 1).
- Dry eyes (Keratoconjunctivitis sicca): decreased tear production, burning, scratchy sensation
- Dry mouth (Xerostomia): dysphagia, difficulty speaking, dental caries, thrush

- Vaginal dryness & dyspareunia
- Parotid gland enlargement
- **Increased risk of (40-fold) lymphoma.**
- Extraglandular Manifestations:
 - Raynaud's phenomenon; Arthritis
 - Interstitial nephritis; type-1 renal tubular acidosis (RTA)
 - Vasculitis; cryoglobulinemia
 - Anemic, leukopenia, thrombocytopenia

III. Management:

- Diagnosis:
 - ANA positive; RF positive (75%)
 - **Anti - Ro (anti-SS-A) positive; Anti - La (anti-SS-B)**
 - **Schirmer test** = filter paper in palpebral fissures to assess tear production
 - **Rose - Bengal staining** = dye that reveals devitalized epithelium of cornea & conjunctiva
 - Biopsy:
 - **Biopsy of lip (minor salivary glands) or parotid gland is the most accurate test.**
 - Biopsy shows lymphocytic infiltration.

R_x

Treatment:

- Ocular = artificial tears, cyclosporin eye drops
- Oral = sugar-free gums, lemon drops, saliva substitute, hydration
- Vaginal dryness = lubricants (K-Y jelly)
- Systemic = NSAIDs, steroids, DMARDs
- Secondary Sjogren's = treat the underlying disease.
- Evaluate for lymphoma

Inflammatory Myopathies:

I. Dermatomyositis:

- It is a non-infectious inflammatory disorder of skin and skeletal muscle.
- **Pathogenesis:**
 - Target = capillaries.
 - Mechanism = antibody mediated damage.
 - It is characterized by immune-complex deposition in blood vessels with complement activation causing skeletal muscle inflammation and weakness + skin involvement.

▪ **Clinical findings:**

- Bilateral symmetrical proximal muscle weakness:
 - Difficulty climbing stairs; arising from chairs, and brushing hair
 - With or without tenderness of the affected area
 - Fever, weight loss and fatigue
- **Grotton's papules:**
 - Pathognomonic skin finding.
 - Violaceous, scaly patches symmetrically over knuckles, elbows, and knees.
- **Heliotrope Eyelids** (purple-red eyelid discoloration with periorbital edema)
- **Shawl Sign** (erythema of face, neck, shoulders, upper chest, and back)
- It may involve:
 - Esophageal muscles = Dysphagia.
 - Lungs = Interstitial lung disease.
 - Blood vessels = Vasculitis.
 - Heart = Myocarditis

▪ **Malignancy:**

- It is associated with three-fold increased risk of malignancy.
- Common sites are:
 - Ovarian – most common
 - Lung
 - Gastrointestinal
 - Lymphoma

▪ **Diagnostic Tests:**

- Creatinine kinase (CK) = elevated
- Aldolase = elevated
- Anti-neutrophilic antibody (ANA) = positive
- **Anti-synthetase (anti-Jo-1) Antibody:**
 - Positive.
 - Its presence is strongly associated with interstitial lung disease.
- Muscle Biopsy:
 - **It is the most accurate investigation.**
 - It shows muscle fibre necrosis, degeneration and regeneration; along with “**perimysial and perivascular inflammation**” (B-cells & CD4 T-cells).

▪ **Treatment:**

- Steroids – mainstay of treatment
- When unresponsive to steroids:

- Methotrexate
- Azathioprine
- Intravenous immunoglobulin
- Mycophenolate.

II. Polymyositis:

- It is a non-infectious inflammatory disorder of skeletal muscle, with no cutaneous involvement.
- Clinical features = same as that of dermatomyositis, except for the skin findings.
- Treatment = same as that of dermatomyositis.
- **Pathogenesis:**
 - Mechanism = T-cell mediated damage causing skeletal muscle inflammation & weakness.
 - Cells responsible = CD8+ T-cells and macrophages
- **Diagnostic Tests:**
 - CK = elevated
 - Aldolase = elevated
 - Anti-neutrophilic antibody (ANA) = positive
 - **Anti-synthetase (anti-Jo-1) Antibody**
 - **Anti – SRP (signal recognition peptide)**
 - Muscle Biopsy:
 - **It is the most accurate investigation.**
 - It shows muscle fibre necrosis, degeneration and regeneration; along with “**endomysial inflammation**”(CD8 T-cells).

Fibromyalgia:

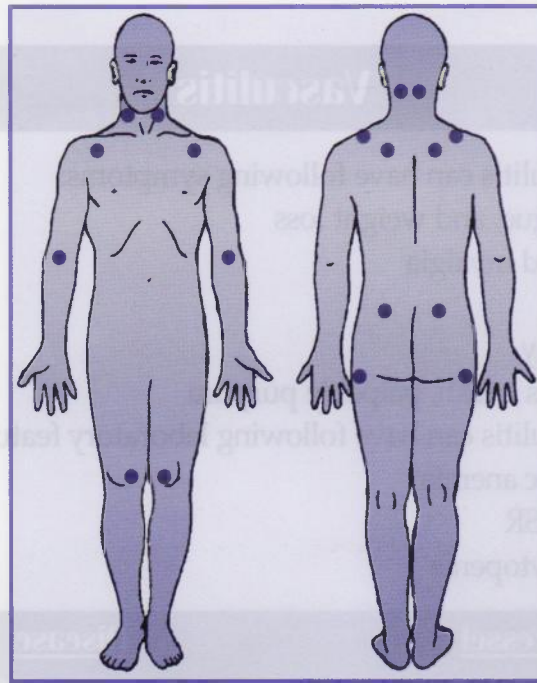
I. Introduction:

- It refers to multiple, regional pain and disability, which is commonly associated with medically unexplained symptoms in other systems.
- It has strong female predominance of around 10: 1.
- **Risk Factors:**
 - Important risk factors are psychosocial distress such as:
 - History of child abuse
 - Marital disharmony
 - Alcoholism in family
 - Physical abuse
- **Pathogenesis:**
 - It has unknown cause.

- It is associated with following findings:
 - (i). Sleep abnormality:
 - **Reduced delta-waves of non-rapid eye movement (non-REM).**
 - Delta waves are characteristic of deep stages of non-REM.
 - Delta waves occur in the first few hours & have restorative function.
 - It is thus considered as a non-restorative sleep disorder.
 - (ii). Abnormal Pain Processing:
 - **Reduced threshold to pain perception and tolerance at characteristic sites throughout the body (see image below).**
 - **Allodynia** i.e. a normally non-noxious stimuli becomes painful.
 - Abnormal central pain processing:
 - Demonstrated by CSF levels of:
 - **Increased Substance P**
 - **Decreased Serotonin**
 - Decreased basal levels of cerebral flow in the caudate & thalamus.
 - Low basal free cortisol & reduction in evening trough

II. Clinical Features:

- Multiple regional pain, often focusing on the neck and back – main feature
- The pain is diffuse and unresponsive to analgesics and NSAIDs.
- The pain is often worsened by physiotherapy.
- Fatigability is most prominent in the morning.
- Diagnosis:
 - Pain is chronic i.e. > 3 months
 - Pain is widespread (i.e. involves right and left sides, above & below waist)
 - Absence of inflammation
 - Presence of pain on palpation of **at least 11/18 “tender points”** such as.
 - Costochondral junction of 2nd rib
 - 1 cm distal to lateral epicondyle of humerus.
 - Mid-gluteal region
 - Medial fat pad of knee (upper medial tibia)
 - Additional Symptoms:
 - Non-throbbing bifrontal headache – tension headache
 - Irritable bowel syndrome
 - Irritable bladder – bladder fullness, nocturnal frequency
 - Chemical sensitivity – frequent side-effects with drugs



Fibromyalgia: Tender Points

III. Investigations:

- There are no abnormalities on routine blood tests and imaging.
- However, it is important to screen for other conditions.
- Following is a list of minimum investigations to screen in fibromyalgia:
 - CBC – to rule out anemia,
 - ESR & CRP – to rule out inflammatory diseases
 - TFTs – to rule out hypothyroidism
 - Ca, Alkaline phosphatase – to rule out hyperparathyroidism, osteomalacia
 - ANA – to rule out SLE

IV. Management:

- Education of patient and their family:
 - Explain that it is relapsing and remitting condition.
 - Reassure that there is no underlying pathology.
 - Cognitive – behavioral therapy
 - Long-term graded exercise programs
- Pharmacologic Management:
 - Low-dose tricyclic anti-depressants – Amitriptyline ± Fluoxetine
 - Alternative Agents (limited data on their efficacy)
 - Tramadol
 - Serotonin-norepinephrine reuptake inhibitors (SNRI) – Duloxetine
 - Anti-convulsants – pregabalin, gabapentin

Vasculitis

- All forms of vasculitis can have following symptoms:
 - Fever, fatigue, and weight loss
 - Malaise and myalgia
 - Joint pain,
 - Neuropathy
 - Skin lesions – rash, palpable purpura
- All forms of vasculitis can have following laboratory features:
 - Normocytic anemia
 - Elevated ESR
 - Thrombocytopenia

<u>Size of Vessel</u>	<u>Disease</u>
Large Vessel Vasculitis	1. Giant cell arteritis 2. Takayasu's arteritis
Medium Vessel Vasculitis	1. Classic polyarteritis nodosa 2. Kawasaki disease
Small Vessel Vasculitis	1. Microscopic polyangitis 2. Wegner's granulomatosis 3. Churg-Strauss syndrome 4. Henoch-Schönlein purpura

I. Giant Cell Arteritis (GCA) & Polymyalgia Rheumatica (PMR):

- GCA is also known as “temporal arteritis”.
- GCA is a granulomatous large-vessel vasculitis of aorta and its branches with predilection for temporal artery.
- GCA affecting cranial branches of aortic arch.
 - Superficial temporal arteries (most common)
 - Ophthalmic arteries
- **Clinical Features:**
 - It is a disease of elderly (age >50 years)
 - It has female predominance.
 - Fever, weight loss, malaise
 - Temporal Artery – ipsilateral headache, tender artery and scalp, absent TA pulse
 - Ophthalmic Artery – optic neuritis, diplopia, amaurosis fugax, blindness

- Facial arteries – jaw claudication (pain on chewing due to ischemia of masseter muscle)

- **Polymyalgia Rheumatic (PMR):**

- It is seen in 50% of patients with giant cell arteritis.
- It presents with:
 - Symmetrical muscle pain & stiffness affecting shoulder & pelvic girdles.
 - Muscles may be tender on palpation.
 - Muscle weakness and wasting are ABSENT.
 - Elevated ESR > 40 mm/h.

- **Diagnosis:**

- Elevated ESR - the typical lab abnormality.
- Elevated CRP
- Normocytic, normochromic anemia
- **Diagnosis is based on clinical features + elevated ESR + prompt response to steroid.**
- **Temporal artery biopsy:**
 - It is the most accurate investigation.
 - It is performed if there is doubt concerning the diagnosis of GCA.
 - It shows fragmentation of internal elastic lamina with necrosis of the media in combination with a mixed inflammatory cell infiltrate.
 - A negative biopsy does NOT rule out the diagnosis

- **Management:**

- Treatment:
 - **PMR = low dose steroids (20 – 30 mg/day)**
 - **GCA:**
 - **Do not await biopsy & pathology reports to start steroids.**
 - High dose steroids (60 – 80 mg/day), then taper slowly.
 - If vision threatened consider IV steroids.
 - **Monitor = clinical status & ESR**
 - Steroid-Sparing Agents (methotrexate, azathioprine) should be considered in patients requiring maintenance dose of steroids > 7.5 mg prednisolone daily.



Clinical Pearl:

Proximal Muscle Weakness:

- Proximal muscle weakness + elevated ESR + **normal CK** = **polymyalgia rheumatica**
- Proximal muscle weakness + elevated ESR + **elevated CK** = **Polymyositis**
- Proximal muscle weakness + elevated ESR + **elevated CK** + **skin involvement** = **Dermatomyositis**.
- Proximal muscle weakness + **normal ESR** + **elevated CK** = **hypothyroidism**
- No muscle weakness + Muscle Pain (tender points) + **normal ESR** + **normal CK** = **fibromyalgia**

II. Takayasu Arteritis:

- It is granulomatous large vessel vasculitis affecting the aorta and its branches.
- **It most commonly affects subclavian and innominate arteries (>90%).**
- It also affects coronary, carotid, renal, and pulmonary arteries.
- **Clinical Features:**
 - **Most common in Asians.**
 - Age of onset = < 50 years (25 – 30 years)
 - Female predominance of 8: 1.
 - Fatigue, malaise, weight loss, arthralgia
 - **Loss of pulse in upper extremities**
 - **Systolic BP difference > 10 mmHg between arms.**
 - Bruit over subclavian arteries or aorta
 - Visual field defects and retinal hemorrhages
- **Diagnosis:**
 - Anemia (normocytic, normochromic) and raised ESR
 - Arteriography (angiography):
 - **It is the most accurate test.**
 - **It shows occlusion, stenosis, irregularity, and aneurysms.**
 - It classifies the diseases into 4 types:
 - Type-I = localized to aorta and its branches.
 - Type-II = localized to descending thoracic & abdominal aorta
 - Type-III = combines features of type-I and II.
 - Type-IV = involves the pulmonary artery
- **Treatment:**
 - High dose steroids ± immunosuppressants (azathioprine, methotrexate)
 - Anti – TNF therapy is the second-line agent.
 - Aspirin
 - Surgical (endovascular) revascularization
 - 5 – Years survival rate = 83%.

III. Kawasaki Disease:

- Also known as “mucocutaneous lymph node syndrome”.
- It is the most common vasculitis in children less than 4 years old.
- It is necrotizing vasculitis involving medium-sized vessels, most commonly the coronary arteries.
- It occurs most commonly in Asians (Japan – most common)
- **Clinical Features:**
 - Fever $> 104^{\circ}\text{F}$ for > 5 days, PLUS:
 - 4 out of 5 following criteria (mnemonic: **CRASH**):
 - Conjunctivitis (bilateral)
 - Rash, primarily truncal
 - Asymmetric cervical lymphadenitis
 - Strawberry tongue, crusting of lips, fissuring of mouth & oropharyngeal erythema.
 - Hands and feet show edema and desquamating rash
 - Complications:
 - Coronary arteritis
 - Myocardial infarction
 - Transient coronary dilatation
 - Pericarditis
 - Perirpheral vascular disease
- **Management:**
 - High dose aspirin (5 mg/kg x 14 days) PLUS:
 - Intravenous immune globulin (IVIG) 400 mg/kg x 4 days.
 - Kawasaki is only one few pediatric (febrile) diseases in which aspirin is given (risk of Reye’s syndrome).
 - Steroids are contraindicated (danger of coronary vessel rupture).
 - Add warfarin if risk for thrombosis is high (very high platelet count)

IV. Polyarteritis Nodosa (PAN):

- It is necrotizing vasculitis involving medium-sized vessels.
- It affects young adults and more men than women.
- It SPARES the pulmonary arteries (if there is lung involvement, suspect other diagnosis)
- **Clinical Features:**
 - Constitutional = weight loss, fever, fatigue
 - Musculoskeletal = myalgias, arthralgias, arthritis
 - Renal = hypertension, renal failure

- CNS = peripheral neuropathies, mononeuritis multiplex, stroke
- GI and GU = abdominal pain, cholecystitis, testicular pain
- Skin = palpable purpura, ulceration, livedo reticularis.



Clinical Pearl: **Mononeuritis Multiplex:**

- Mononeuritis multiplex refers to involvement of ≥ 2 peripheral nerves.
- Mononeuritis multiplex is caused by systemic conditions like PAN, AIDS, Diabetes, leprosy.
- Example: combination of radial nerve palsy (wrist drop) and common peroneal nerve palsy (foot drop).

▪ **Management:**

- Lab Findings:
 - Elevated ESR and CRP.
 - **Hepatitis B surface antigen (HBsAg) is positive in 30% cases.**
 - **No association with antineutrophil cytoplasmic autoantibodies (ANCA).**
- Diagnosis:
 - Angiography:
 - It is performed on mesenteric or renal vessels.
 - **It shows areas of dilatation and constriction (beading-appearance)**
 - CT Angiography:
 - It may be adequate to make the diagnosis.
 - However, angiography is the most sensitive test.
 - Biopsy:
 - It is the most accurate test – sural nerve, skin, or affected organ.
 - **It shows vasculitis with fibrinoid necrosis WITHOUT granuloma.**
- Treatment:
 - Corticosteroids and cyclophosphamide
 - Anti-viral therapy for hepatitis B – related PAN.

V. Microscopic Polyangiitis:

- It is necrotizing vasculitis involving small vessels i.e. arterioles, capillaries, and venules.
- It is not associated with hepatitis B (unlike PAN).
- Involves pulmonary capillaries (unlike PAN).
- It is associated with perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA) in 70% cases.
- **Clinical Features:**
 - Pauci-immune glomerulonephritis
 - Pulmonary capillary alveolitis – pulmonary hemorrhage, hemoptysis
 - Dermal leukocytoclasticvenulitis – palpable purpura
- **Treatment:**
 - Cyclophosphamide and high-dose steroids.
 - Azathioprine is used for maintenance.

VI. Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis):

I. Introduction:

- It is a necrotizing granulomatous systemic vasculitis, commonly involving upper respiratory tract, pulmonary and renal vessels.
- **Clinical features:**
 - Males > Females.
 - Age = 40 – 60 years
 - Upper Respiratory:
 - Sinusitis; Otitis media
 - Rhinitis, nasal mucosal ulceration, saddle-nose deformity
 - Oral ulcers, nasal ulcers, hearing loss
 - Lower Respiratory:
 - Migratory pulmonary infiltrates and nodules in 50% of cases.
 - Pulmonary hemorrhage, and pleurisy
 - Hemoptysis, nodular lesions on chest x-ray.
 - Renal:
 - Proteinuria, hematuria, red cell casts
 - Focal necrotizing glomerulonephritis (mild form)
 - Rapidly progressive (crescentic) glomerulonephritis (RPGN) (severe form)

○ Other Systems:

- Ocular - episcleritis, scleritis, uveitis, orbital granulomas
- Neurologic - cranial and peripheral neuropathies
- Skin - palpable purpura, livedo reticularis

II. Diagnosis & Management:

Diagnosis:

- Active Disease:
 - Leukocytosis, elevated ESR, CRP
 - Elevated serum c – ANCA.
- CXR or CT chest = nodules, infiltrates, cavities.
- Increased BUN and creatinine, proteinuria, hematuria, dysmorphic RBCs.
- Biopsy (either lung, kidney, or sinus):
 - It is the most accurate test.
 - It shows necrotizing inflammation of arterioles, capillaries, and venules.

Treatment:

- Induction:
 - Cyclophosphamide + high-dose steroids – OR –
 - Rituximab + high-dose steroids
- Maintenance:
 - Methotrexate or Azathioprine ≥ 2 years after cyclophosphamide induction
 - If rituximab is used for induction, repeat it after 6 months of maintenance.

VII. Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome):

I. Introduction:

- It is a small vessel vasculitis involving skin, lung, and heart vessels.
- It is similar to Wegener's granulomatosis with more frequent cardiac involvement associated with asthma and eosinophilia.
- **Clinical Features:**
 - Asthma (new asthma in an adult should always raise suspicion)
 - Allergic rhinitis
 - Glomerulonephritis
 - Mononeuritis multiplex
 - Cardiac involvement = myocarditis, coronary arteritis, CHF.

- Classic Triad:
 - Skin lesion (purpura or nodules)
 - Asymmetric mononeuritis multiplex
 - And eosinophilia on a background of resistant asthma.

II. Diagnosis & Management:

■ Diagnosis:

- Migratory pulmonary infiltrates on CXR.
- ANCA positive (either c-ANCA or p-ANCA).
- Eosinophilia
- Biopsy:
 - It is the most accurate test.
 - It shows granulomatous inflammation, necrosis and thrombosis of small arteries and veins with eosinophilic infiltrate.

■ Treatment:

- Induction - High-dose steroids + Cyclophosphamide (if severe)
- Maintenance - Low-dose steroids + azathioprine, methotrexate, or mycophenolate



Clinical Pearl:

Anti-neutrophil Cytoplasmic Antibody (ANCA):

- It is of two types:
 1. Cytoplasmic ANCA i.e. c-ANCA also called "Anti-proteinase-3 antibodies"
 2. Perinuclear ANCA i.e. p-ANCA also called "Anti-myeloperoxidase antibodies".
- c-ANCA = Wegener's granulomatosis
- p-ANCA = Microscopic polyangiitis
- Both c-ANCA & p-ANCA = Churg – Strauss syndrome

VIII. Buerger Disease:

- Also known as "thromboangiitis obliterans".
- It is medium-sized vessel vasculitis with digital vessel thrombosis.
- Most common site = tibial and radial arteries (most common)
- Gender = common in men, but increasingly reported in women.
- Associations:
 - Smoking
 - HLA-A9 and HLA-B5

▪ **Complications:**

- Foot claudication
- Ulceration of toes or fingers
- Gangrene, auto-amputation
- Severe pain, even at rest.

▪ **Management:**

- Smoking cessation
- Intravenous iloprost (prostaglandin analogue)

IX. Henoch-Schonlein Purpura:

- It is a small vessel vasculitis involving skin, GI, renal and joint vessels.
- It is most common form of childhood systemic vasculitis.
- Epidemiology: male > female, children > adults, winter > summer.
- **Clinical Features:**
 - Often follows a viral upper respiratory infection.
 - **Palpable purpura on extensor surfaces** – buttocks and lower extremities.
 - **Colicky abdominal pain**; intussusception
 - **Polyarthritis (non-deforming)** – hips, knees, ankles
 - Nephriti – **microscopic hematuria**, proteinuria
 - Fever
- **Diagnosis:**
 - **Skin biopsy = leukocytoclastic vasculitis with IgA and C3 deposition in vessel wall.**
 - Renal biopsy = mesangial IgA deposition.
- **Treatment:**
 - Supportive (often self-limiting over 4 weeks)
 - Steroids with or without DMARDs for renal or severe disease

X. Behcet's syndrome:

- It is vasculitis of unknown etiology that characteristically targets venules.
- It is associated with HLA-B51.
- Prevalence = Turkey, other Asian countries.
- **Diagnostic Criteria:**
 - **Recurrent oral ulceration** (at least 3 times in 1 year)
 - Plus 2 of the following features:
 - Recurrent genital ulceration
 - Eye lesions (uveitis, scleritis, retinal vasculitis)
 - Skin lesions (erythema nodosum, pustules, papules, folliculitis)

- **Positive pathergy test** i.e. pricking forearm with sterile needle results in pustule formation within 48 hours.

- **Treatment:**

- Oral ulcerations:
 - Mild = topical steroids; colchicine
 - Severe = azathioprine, thalidomide (teratogenic), methotrexate
- Erythema nodosum and arthralgia = colchicine, NSAIDs, steroids
- Ocular disease (uveitis) = steroids + immunosuppressants (azathioprine, infliximab)
- Neurologic disease = steroids + immunosuppressants

XI. Cryoglobulinemia:

- Cryoglobulinemia is a condition characterized by large amounts of cryoglobulins in blood.
- Cryoglobulins are proteins that precipitate on exposure to the cold.
- **Clinical Features:**
 - Weakness; low-grade fever
 - Dermatologic:
 - Lower extremity purpura; leg ulcers
 - Livedo reticularis
 - Raynaud's phenomenon
 - Leukocytoclastic vasculitis
 - Rheumatologic = symmetric migratory arthralgias of small or medium joints.
 - Renal = glomerulonephritis (proteinuria, hematuria, acute renal failure, HTN, edema)
 - Hematologic = anemia, thrombocytopenia
 - GI = abdominal pain, hepatosplenomegaly, abnormal LFTs,
 - Neurologic = peripheral neuropathy and mononeuritis multiplex

Types:

Feature	Type-I (Monoclonal)	Type-II (Mixed)	Type-III (Polyclonal)
Percentage	25%	25%	50%
Cryoglobulins	Monoclonal Immunoglobulin (IgM or IgG)	Monoclonal IgM (with RF activity) plus Polyclonal IgG	Polyclonal IgG
Common causes	<ol style="list-style-type: none"> 1. Multiple myeloma 2. Waldenstrom's macroglobulinemia 3. NHL 4. HL 5. CLL and CML 6. TTP 7. Myelodysplasia 	<ol style="list-style-type: none"> 1. Hepatitis C 2. Hepatitis B 3. Bacterial (endocarditis, syphilis) 4. Malaria 5. Fungal (coccidiomycosis) 	Autoimmune syndrome: <ol style="list-style-type: none"> 1. SLE 2. Sogren's 3. RA 4. IBD 5. Sarcoidosis 6. PAN
Primary manifestations	Hyper-viscosity with or without thrombosis.	Immune-complex mediated vasculitis, with multi-organ involvement	
Rheumatoid factor	Negative	Positive	Positive
Complement	Normal	Decreased C4	Decreased C4
Serum viscosity	Raised	Normal	Normal

Diagnosis:

- Cryoglobulins:
 - These are proteins that precipitate from "Serum" or "Plasma" when cooled.
 - These are different from cryofibrinogenemia; which are proteins that precipitate from plasma only.
- Positive rheumatoid factor
- False elevation in WBC or platelet count (due to cryoprecipitation)
- Decreased C4 levels, variable C3 levels
- Increased ESR
- In HCV-associated type-2 cryoglobulinemia = + HCV RNA, – anti-HCV Ab
- Biopsy of affected tissue (skin, kidney)

Treatment:

- Treat the underlying disorder e.g:
 - Anti-viral therapy ± rituximab for HCV
 - DMARDs for rheumatic disease.
- NSAIDs for control of mild symptoms for patients with normal renal function
- Prednisolone + immunosuppressants for major organ involvement
- Plasmapheresis in severe cases.

Diseases of Bone

Paget's Disease:

I. Introduction:

- Also known as “osteitis deformans”.
- It is a localized **disorder of bone remodeling** due to osteoclast dysfunction.
- It may be caused by a slow virus infection by paramyxovirus.
- **Pathogenesis:**
 - Increased osteoclastic bone resorption.
 - Osteoclasts are increased in number, and contain characteristic nuclear inclusion bodies.
 - Increased osteoblastic activity.
 - Mutations in SQSTM1 gene.
 - It mostly affects the axial skeleton:
 - Pelvis
 - Femur, tibia, lumber spine, skull.
- **Clinical features:**
 - Bone pain is the most common symptom.
 - Hypervascularity warms the overlying skin.
 - Increased head size and platybasia (invagination of base of skull).
 - Deafness:
 - It results from compression of the auditory nerve.
 - It is however, conductive deafness due to osteosclerosis of temporal bone.
 - Complications:
 - High-output cardiac failure.
 - Osteoarthritis
 - **Osteosarcoma:**
 - It is a rare, but serious complication.
 - It presents with subacute, increasing pain & swelling of the affected side.

II. Diagnosis & Management:

- **Lab Findings:**
 - Increased serum alkaline phosphatase (ALP)
 - Increased urinary excretion of hydroxyproline.
 - Serum calcium = normal
 - Serum phosphate = normal.
 - X-ray of bone:
 - Bone expansion,
 - With alternating areas of radiolucency and osteosclerosis.

▪ **Treatment:**

- The main indication for treatment is bone pain.
- **Bisphosphonates are the mainstay of treatment.**
- If symptoms improve with bisphosphonates, the pain is due to metabolic activity.
- If symptoms don't improve, then the pain is due to a complication & should be addressed accordingly.
- Bisphosphonates are of two types:
 - Simple bisphosphonates:
 - These are less effective.
 - These agents are for example, etidronate and tiludronate.
 - Amino-bisphosphonates:
 - These are more effective.
 - These agents are for example, pamidronate, and risedronate.
- Calcitonin can also be used due to its inhibitory effect on bone turnover.
- Calcitonin is given subcutaneously (100 – 200 U x 3 times weekly)

Rickets & Osteomalacia:

I. Introduction:

- Rickets (in children) and Osteomalacia (in adults) result from inadequate mineralization of bone matrix (osteoid).
- They are usually caused by a defect in vitamin D availability or metabolism.

▪ **Rickets:**

- It occurs in children prior to closure of the epiphyses.
- It is characterized by following main features:
 - Craniotabes i.e. soft skull bones
 - Widening of wrist joints.
 - Bowing of legs
 - Pigeon chest deformity
 - Lumbar lordosis
 - Harrison's sulcus (a groove in the rib cage)
 - Rachitic rosary i.e. defective mineralization and overgrowth of epiphyseal cartilage in ribs.

▪ **Osteomalacia:**

- It occurs in adults, most commonly during pregnancy and lactation.
- It is characterized by following main features:
 - Bone pain
 - Muscle pain
 - Fractures of vertebrae, hips, and wrist

- Occasionally a marked proximal myopathy leads to a characteristic "waddling-gait".

II. Causes:

Vitamin D Deficient Rickets:

- Lack of sunlight exposure – most common
- Low dietary intake
- Malabsorption:
 - Celiac disease
 - Intestinal resection
- Pathogenesis:
 - Deficiency of vitamin D (both calcidiol i.e. 25(OH) D₃ and calcitriol i.e. 1, 25(OH)₂D₃) impairs intestinal calcium absorption and lowers serum calcium.
 - Decreased serum calcium stimulates PTH secretion.
 - PTH causes increased serum calcium (hypercalcemia) by increasing bone resorption increased urinary phosphate excretion (hypophosphatemia).
 - This results in progressive demineralization of bone.

Vitamin D Resistant Rickets:

- It is of two types:
 - Type-I is due to low renal 1 α -hydroxylase activity resulting in impaired conversion of 25-hydroxy vit.D₃ to 1,25-dihydroxy-vitamin D₃.
 - Type-II has end-organ resistance to 1,25-dihydroxy-vitamin D₃, due to a point mutation in the receptor.

Hypophosphatemic Rickets:

(i). Inherited Causes:

- It is a group of inherited condition characterized by defective renal phosphate reabsorption
- Mutations:
 - X-linked = PHEX gene
 - Autosomal dominant = FGF23 gene
 - Autosomal recessive = DMP1 gene

(ii). Acquired Causes:

- Tumor-induced hypophosphatemicostemalacia:
 - Also called "Oncogenic Hypophosphatemia".
 - It is due to increased production of phosphatonin fibroblast growth factor-23 (FGF23 gene).
 - It causes hyperphosphaturia and decreased serum phosphate levels.

- Other Causes:
 - Renal osteodystrophy – due to 1,25-dihydroxy-cholecalciferol deficiency
 - Drug induced (e.g. anti-convulsants)
 - Vitamin D resistance
 - Liver disease

III. Diagnosis:

- Vitamin D Deficiency:
 - Decreased serum Ca, decreased PO₄
 - Increased PTH, increased alkaline phosphatase
 - 25-hydroxy vitamin D is decreased
 - In renal failure 1,25 dihydroxy-vitamin D is decreased
- Vitamin D Resistant Rickets:
 - Type I is similar to vitamin-D deficiency except that 25-hydroxy vitamin D is normal.
 - Type II is different from Type-I and vitamin D deficiency:
 - 25, hydroxyl vitamin D is normal
 - Increased PTH; increased 1,25-dihydroxy vitamin D₃
- Hypophosphatemic Rickets:
 - Hypophosphatemia and phosphaturia
 - Raised alkaline phosphatase; and absence of vitamin D deficiency.

IV. Treatment:

- In dietary deficiency, given vitamin D supplements.
- In malabsorption or liver disease, give vitamin D₂ (ergocalciferol) 250 – 1000 µg daily parenteral calcitriol.
- Type-I vitamin D resistance, give:
 - 1α-hydroxy vitamin D₃ = 1 – 2µg daily. OR
 - Calcitriol (1,25-dihydroxy-vitamin D₃) 250ng - 1µg daily
- Type-II vitamin D resistance, give:
 - High doses of vitamin D (i.e. 1α-hydroxy vitamin D₃ or calcitriol), PLUS
 - Calcium and phosphate supplements
- Hypophosphatemic Rickets:
 - Phosphate supplements 1 – 4 g daily, PLUS
 - 1α-hydroxy vitamin D₃ = 1 – 2µg daily. OR
 - Calcitriol (1,25-dihydroxy-vitamin D₃) 250ng - 1µg daily

Osteoporosis:

I. Introduction:

- It is the most common metabolic bone disease.
- The defining feature of osteoporosis is reduced bone mineral density.
- This leads to micro-architectural deterioration of bone tissue & increased risk of fracture.
- **Pathophysiology:**
 - Osteoporosis occurs due to:
 - Defect in attaining peak bone mass
 - Accelerated bone loss
 - Estrogen deficiency is the main factor in post-menopausal osteoporosis.
 - Estrogen deficiency results in bone resorption (osteoclasts) exceeding bone formation (osteoblasts).
 - Senile osteoporosis is due to decreased bone formation.
 - Genetic factors play an important role in the pathogenesis.
 - Environmental Factors:
 - Smoking
 - Heavy alcohol consumption

II. Etiology:

- Post-menopausal – most common
- Corticosteroid-induced – **(risk increased if prednisolone >7.5 mg daily for ≥ 3 months)**
- Secondary Causes:
 - Endocrine Diseases:
 - Hypogonadism – testosterone deficiency results in increased bone turnover
 - Hyperparathyroidism
 - Hyperthyroidism
 - Cushing's syndrome
 - Gastrointestinal:
 - Malabsorption Syndromes
 - Chronic liver disease
 - Medications:
 - Steroids, GnRH agonists
 - Aromatase inhibitors, Anti-convulsants
 - Alcohol intake > 3 U/day, Heparin
 - Thyroxine, Thiazolidinediones
 - Miscellaneous:
 - Multiple Myeloma, HIV infection
 - BMI < 18, Heavy smokers
 - Immobilization, Anorexia Nervosa

III. Diagnosis:

- **Clinical Features:**

- It is asymptomatic until a fracture occurs.
- Vertebral Fractures:
 - Gradual onset of chronic pain, height loss, and kyphosis
 - Acute-onset back pain
 - Pain aggravated by movement, localized tenderness
 - Pain radiates to anterior chest, buttocks, thighs.
- Hip fracture – pain, leg is shortened & externally rotated
- Peripheral fractures – local pain, tenderness, deformity

- **Diagnosis:**

- **Dual Energy X-ray Absorptiometry (DEXA) is the most accurate test.**
- Indications:
 - Low-trauma fracture age > 50 years
 - Clinical features of osteoporosis – height loss, kyphosis
 - Osteopenia on plain x-ray
 - Steroid therapy
 - Family history of hip fracture
 - Low BMI (< 18)
 - Early menopause (< 45 y)
- Other Tests:
 - Serum Ca, Vitamin D, PTH
 - Renal function, LFTs, TFTs, ESR, Anti-TTG antibodies (celiac disease)

III. Management:

- Smoking cessation
- Alcohol intake in moderation
- Indications for Medications:
 - **Bone mineral density (BMD) T – Score < – 2.5**
 - **BMD T – Score < – 1.5 in corticosteroid-induced osteoporosis**
- **Bisphosphonates:**
 - These inhibit bone resorption by binding to hydroxyapatite crystals on bone surface
 - Oral bisphosphonates are poorly absorbed from gastrointestinal tract.
 - **Therefore, they should be taken on empty stomach with plain water, and no food should be eaten for 30 – 45 minutes.**
 - Oral Agents – Alendronate, Risedronate, Ibandronate
 - IV agents – Ibandronate, Zoledronate

- Side-Effects:
 - Most Common:
 - Upper GI intolerance – oral agents
 - Transient influenza-like illness – IV agents
 - Atrial fibrillation (IV zoledronate)
 - Uveitis
 - **Osteonecrosis of the Jaw:**
 - It is characterized by necrotic bone in mandible or maxilla.
 - It occurs after tooth extraction.
 - Risk Factors – cancer, diabetes, infection, high-doses of bisphosphonates
 - Patients must pay attention to good oral hygiene.
 - Stopping bisphosphonates before tooth extraction is NOT protective.
- **Denosumab:**
 - It is a monoclonal antibody that neutralizes the effect of RANKL.
 - It is given SC every 6 months.
 - It is a powerful inhibitor of bone resorption.
 - It reduces the risk of:
 - Hip fracture - 40%
 - Vertebral fracture - 70%
 - Non-vertebral fracture - 20%
- **PTH:**
 - It stimulates new bone formation.
 - Agent: Teriparatide (20 µg SC injection x once daily)
 - Recommended duration of treatment is 24 months.
 - It is expensive with main indications are:
 - Severe osteoporosis (T – Score < – 3.5 to – 4.0)
 - Failure to respond with other treatments
- **Other Agents:**
 - Calcium & Vitamin D
 - Strontium ranelate
 - Hormone replacement therapy (HRT)
 - Selective Estrogen Receptor Modulators (SERMS) – Raloxifene:
 - It is a partial agonist at estrogen receptors in bone & liver
 - It is an antagonist at estrogen receptors in breast & endometrium.

- It is associated with increased risk of venous thromboembolism (like HRT)
- It reduces the risk of breast cancer.
- Calcitonin:
 - It is an osteoclast inhibitor.
 - It is no longer recommended for osteoporosis – risk of cancer

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Chapter 13

NEUROLOGY



Cerebrovascular Diseases

Stroke:

I. Introduction:

▪ Definitions:

- **"Stroke"** – refers to sudden onset of focal neurologic deficit lasting > 24 hours or leading to death, with no cause apparent other than a vascular one.
- **"Transient Ischemic Attack [TIA]"** – refers to sudden onset of focal neurologic deficit lasting < 24 hours with complete recovery.
- **"Stroke in Evolution"** – refers to stroke in which focal neurologic deficit worsens after the patient first presents.
- **"Completed Stroke"** – refers to a stroke in which focal neurologic deficit persists and is not progressing.

▪ Classification:

- Stroke can be classified into two types:
 - Ischemic Stroke (85%)
 - Hemorrhagic Stroke (15%):
 - Intra-parenchymal Hemorrhage (IPH)
 - Subarachnoid hemorrhage (SAH)

▪ Risk Factors:

- Non-modifiable:
 - Age
 - Gender (male > female)
 - Race (Afro-Caribbean > Asian > European)
 - Previous vascular event (MI, stroke)
- Modifiable:
 - Hypertension
 - Diabetes mellitus
 - Hyperlipidemia
 - Heart disease – AFib, CHF, Infective Endocarditis



- Smoking
- Alcohol
- Polycythemia
- Estrogen-containing Drugs:
 - Oral contraceptives
 - Hormone replacement therapy

II. Transient Ischemic Attack (TIA):

- It is characterized by sudden onset focal neurologic deficit due to cerebral ischemia.
- There is no stroke on imaging & symptoms resolve within 24 hours (mostly < 1 hour).
- Risk of Subsequent Stroke – **Mnemonic: ABCD²**

<u>ABCD²</u>	<u>Score</u>
<u>A</u> ge ≥ 60 years	+ 1
<u>B</u> P ≥ 140/90	+ 1
<u>C</u> linical Features: <ul style="list-style-type: none"> ▪ Unilateral Weakness ▪ Speech impairment WITHOUT weakness 	+ 2 + 1
<u>D</u> uration: <ul style="list-style-type: none"> ▪ ≥ 60 mins ▪ 10 – 59 mins 	+ 1 + 1
<u>D</u> iabetes	+ 1
Risk of Stroke at 48 Hours: <ul style="list-style-type: none"> ▪ Low risk (0 – 3) = 1% ▪ Moderate risk (4 – 5) = 4.1% ▪ High risk (6 – 7) = 8.1% 	

III. Ischemic Stroke:

- Cerebral infarction (ischemic stroke) is due to inadequate blood flow to part of the brain due to occlusion of the cerebral artery.

(i). Introduction:

- **Pathophysiology:**
 - Ischemia causes cell hypoxia and depletion of cellular adenosine triphosphate (ATP).
 - Without ATP, there is no longer the energy to maintain ionic gradients across the cell membrane and cell depolarization.
 - Cytotoxic edema subsequently develops due to:
 - Influx of sodium and calcium ions
 - Passive inflow of water into the cell

Clinical Pearl:**Ischemic Core & Penumbra:**

- Ischemic Core:
 - Affected regions of ischemia with cerebral blood flow of lower than 10 mL/100 g of tissue/min are referred to collectively as the core.
 - These cells are presumed to die within minutes of stroke onset.
- Ischemic Penumbra:
 - Affected regions with decreased or marginal perfusion (cerebral blood flow < 25 mL/100g of tissue/min) are collectively called the ischemic penumbra.
 - These cells can remain viable for several hours because of marginal tissue perfusion.

▪ **Causes:**

- Thrombotic Disease:
 - It accounts for 55% of cerebral infarction.
 - It is mostly secondary to atherosclerosis in major extra-cranial arteries – carotid artery & aortic arch.
- Embolic Disease:
 - Cardiogenic embolism – 20%:
 - Valvular thrombi – (MS, endocarditis, prosthetic valve)
 - Mural thrombi – (MI, AFib, CHF, dilated cardiomyopathy)
 - Atrial myxoma
 - Extracranial arteries – e.g. aortic arch
 - Paradoxical Embolism (PDE):
 - PDE originates from a “venous” thrombosis.
 - The most common source is DVT of the lower extremities.
 - The thrombus enters the “arterial” circulation through an intra-cardiac communication, such as:
 - Patent foramen ovale [PFO] – most common
 - ASD, VSD, PDA, Ebstein anomaly
- Lacunar Stroke:
 - It is caused by occlusion of deep penetrating branches of cerebral artery.
 - It accounts for 20% of infarctions, mostly commonly related to hypertension.
 - “Lacunes” – small subcortical infarcts (< 15 mm) in the territory of deep penetrating arteries.
 - Causes:
 - Microthrombi
 - Lipohyalinosis
 - Hyaline arteriosclerosis
 - Amyloid angiopathy
 - Microemboli

(ii). Clinical Features:

- Clinical features depend upon which arterial territory is involved and the size of the lesion.
- Cerebral Artery & Features:
 - **Anterior Cerebral Artery (ACA):**
 - **Contralateral weakness and sensory loss in legs > arms.**
 - **Confusion and behavioral disturbances.**
 - Urinary incontinence.
 - Face is spared.
 - If bilateral; motor inertia and muteness.
 - **Middle Cerebral Artery (MCA):**
 - **Contralateral hemiplegia**
 - **Contralateral hemi-sensory loss mainly of face and arm.**
 - Visual field defect (contralateral homonymous hemianopia)
 - If dominant hemisphere (left MCA) = aphasia.
 - Broca's aphasia = If problem in speech production
 - Wernicke's aphasia = If problem is speech comprehension
 - If non-dominant hemisphere (right MCA):
 - Visuospatial disturbance
 - Example: patient cannot dress, gets lost
 - **Posterior Cerebral Artery (Posterior Circulation):**
 - Supplies the occipital lobe.
 - Contralateral homonymous hemianopia with macular sparing
 - Visual hallucinations
 - Visual agnosia (inability to recognize or discriminate)
 - **Vertebro-Basilar Circulation (Posterior Circulation):**
 - Supplies cerebellum, brainstem, and occipital lobe.
 - Vertebral Artery (**Wallenberg syndrome**):
 - **Sensory loss of ipsilateral face and contralateral limbs.**
 - Diplopia, dysarthria, ipsilateral Horner's syndrome
 - Basilar Artery:
 - **Pupillary Changes = Midbrain – dilated pupils, Pons – pinpoint**
 - Quadriplegia and sensory loss
 - Cranial nerve palsies
 - **"Locked-in Syndrome"** i.e. aware but no response (basilar artery)
 - Cerebellar Artery:
 - Vertigo, nausea, vomiting, diplopia, and nystagmus
 - Ipsilateral limb ataxia

- **Lacunar Stroke:**

- It is associated with 5 major syndromes:
 - Pure motor weakness (pure hemiplegia)
 - Pure sensory loss (pure hemianesthesia)
 - Dysarthria – Clumsy hand syndrome
 - Ataxic hemiparesis
 - Mixed sensimotor



Clinical Pearl:

Hemiplegia:

- **Uncrossed Hemiplegia:**
 - It refers to contralateral hemiplegia + contralateral cranial nerve palsy (facial nerve).
 - It results from lesions ABOVE brainstem i.e. of cerebral cortex or internal capsule.
- **Crossed Hemiplegia:**
 - It refers to contralateral hemiplegia + ipsilateral cranial nerve palsy (facial nerve).
 - It results from lesions of the brainstem i.e. midbrain, pons, medulla oblongata



Clinical Pearl:

Posterior Circulation Strokes:

- Posterior circulation strokes are associated with 4 “Deadly D’s”:
 - Diplopia; dizziness
 - Dysphagia; dysarthria
- **Weber Syndrome:**
 - Ipsilateral cranial nerve III (oculomotor) palsy
 - Contralateral hemiplegia

(iii). Investigations:

- **Non-contrast CT scan:**

- It is the best initial test in patients with stroke.
- It differentiates between hemorrhagic and ischemic stroke.
- It is most sensitive test for detecting blood in the brain, therefore if fails to detect blood, the patient is considered to have ischemic stroke.
- It is often negative for ischemia within the first 48 hours after symptoms onset.

- **Diffusion-weighted MRI:**

- It is the most accurate test for detecting ischemia.
- It detects ischemia earlier than CT.
- It is more sensitive than CT in detecting strokes of brainstem and cerebellum.
- It is however, less readily available and costly as compared to CT scan and therefore not the initial investigation.

▪ **Other Investigations:**

- Underlying Vascular Disease:
 - Duplex ultrasound of carotids
 - Magnetic resonance angiography (MRA)
 - CT angiography (CTA)
- Underlying Cardiac Source:
 - ECG
 - Echocardiogram
- Other Risk Factors:
 - CBC, lipid profile, blood glucose,
 - ESR, serum protein electrophoresis

(iv).

R_x

Treatment of Ischemic Stroke:

▪ **Thrombolysis:**

- Intravenous recombinant tissue plasminogen activator (t-PA):
 - It improves mortality when given within 4.5 hours of symptom onset.
 - It is most effective when given within 3 hours of symptom onset – the earlier the better.
 - If > 4.5 hours of stroke onset – then aspirin only (if no contraindications)
 - If hemorrhagic stroke – NO thrombolysis
 - Contraindications to tPA:
 - Stroke or head trauma – past 3 months
 - Myocardial infarction – past 3 months
 - Gastrointestinal bleeding – within the past 21 days.
 - Genitourinary bleeding – within the past 21 days.
 - Major surgery – within 14 days.
 - Arterial puncture – within 7 days.
 - Lumbar puncture – within 7 days.
 - Laboratory:
 - Platelets = < 100, 000/mm³
 - Serum glucose < 2.8 mmol/L or > 22.2 mmol/L.
 - INR > 1.7 if on warfarin
- Heparin:
 - It doesn't lower mortality.
 - It reduces the risk of recurrent ischemia and venous thromboembolism.
 - It increases the risk of hemorrhage – both intracranial & extracranial.
 - It should therefore be NOT used in routine management of acute stroke.

- **Anti-Platelet Therapy:**

- Aspirin:
 - It should be started immediately after an ischemic stroke.
 - Dosage: 300 mg once, then 75 mg daily.
 - It should be, however, withheld for at least 24 hours if the t-PA is given.
 - It decreases mortality and recurrent stroke.
 - If the patient is already on aspirin, then:
 - Add dipyridamole (200 mg twice daily) – OR –
 - Switch to clopidogrel (75 mg daily)
- Dipyridamole & Clopidogrel:
 - Dipyridamole + aspirin are superior to aspirin alone.
 - Clopidogrel + aspirin are NOT more effective than aspirin alone.

- **Carotid Revascularization:**

- Carotid endarterectomy is surgical procedure for carotid artery revascularization.
- Carotid endarterectomy is associated with 5% risk of stroke.
- Carotid endarterectomy reduces the risk of subsequent stroke if:
 - **Symptomatic ipsilateral stenosis of 70 – 99% - most benefit.**
 - **Asymptomatic ipsilateral stenosis of 70 – 99% and age is < 75 years.**
 - When surgery is performed within the first couple of weeks after stroke.
 - Endarterectomy has NO ROLE for milder stenosis (< 50%).

- **Secondary Preventions:**

- Blood pressure control (using thiazides, ACE inhibitors)
- Diabetes – HbA1C < 7%
- Lipid control:
 - Target LDL < 100 if carotid stenosis is the cause of stroke
 - Use statins – Simvastatin 40 mg.
- Lifestyle Modifications:
 - Smoking cessation
 - Lower salt intake
 - Lower fat intake
 - Lower excess alcohol intake
 - Increase exercise
 - Weight loss

IV. Hemorrhagic Stroke:

- It accounts for 15% of stroke.
- It can be further classified into:
 - Intraparenchymal hemorrhage (IPH) – (aka intracranial hemorrhage [ICH]).
 - Subarachnoid hemorrhage (SAH)

(i). Intraparenchymal Hemorrhage:

- It refers to bleeding within the brain parenchyma due to rupture of a blood vessel.
- **Risk Factors:**
 - Hypertension:
 - It is the most common cause of intracerebral hemorrhage.
 - Sites – putamen (most common), thalamus, pons, and cerebral hemispheres.
 - Other Factors:
 - Arteriovenous malformation (AVM)
 - Amyloid angiopathy
 - Anticoagulation therapy
 - Thrombolytic therapy
 - Tumors
 - Cocaine
- **Clinical Features:**
 - Impairment in level consciousness
 - Vomiting and headache
 - Seizures
 - May cause progressive focal neurologic deficit depending on the site of hemorrhage:
- **Diagnosis & Management:**
 - Non-contrast CT scan – best initial test.
 - MRI
 - Angiography to determine the source of bleeding.
 - Management:
 - Airway protection & intubation if poor airway protection or GCS < 8.
 - Avoid hyperthermia.
 - Head of bed elevation to 30 – 45°.
 - Reverse any coagulopathies:
 - Use with vitamin K, fresh frozen plasma (FFP)
 - Target INR < 1.4
 - Target platelet > 100,000:

- Platelet transfusion – especially if expanding ICH
- DDAVP (desmopressin) – if uremic.
- Strict BP control with arterial line:
 - Target SBP < 160 (< 140 for SAH)
 - Preferred agents: nicardipine, labetalol
- Anti – seizure prophylaxis
- Surgical Decompression:
 - Decompressive hemicraniectomy
 - Indicated for large hemorrhage with clinical deterioration.

(ii). Subarachnoid Hemorrhage (SAH):

- **Causes:**
 - Saccular (Berry) aneurysm (most common)
 - Vascular malformations
 - Hematologic disturbances
 - Tumors
 - Traumatic hematoma
- **Saccular (Berry) Aneurysm:**
 - It is the most common cause of subarachnoid hemorrhage.
 - It is the most common type of intracranial aneurysm.
 - Most common site: anterior circulation (junction of ACA with Anterior communicating artery).
 - Causes:
 - Smoking and hypertension (54%)
 - Adult polycystic kidney disease.
 - Ehlers-Danlos syndrome (Type-IV).
 - Marfan syndrome
 - Neurofibromatosis type I.
- **Clinical Features:**
 - Abrupt-onset, intensely painful “thunderclap” headache.
 - Often described as the “**worst headache of my life**”,
 - Loss of consciousness in 25 – 50% of cases.
 - Signs of meningeal irritation – neck stiffness, photophobia, vomiting.
- **Diagnosis:**
 - Non-contrast CT scan:
 - **It is the best initial test.**
 - It is very sensitive in the initial stages especially within 12 hours of presentation.

- Lumber Puncture:
 - **It is the investigation of choice.**
 - It is performed when CT is negative for hemorrhage, or if presentation is >12 hrs.
 - LP findings:
 - Pressure = increased
 - Color = **Xanthochromia (yellow from RBC hemolysis within CSF)**
 - RBCs = raised
 - WBC = normal – raised
 - Glucose = normal
 - Protein = raised



Clinical Pearl:

WBC: RBC Ratio:

- WBCs can be elevated in CSF of SAH – mimicking meningitis.
- In meningitis the ratio of WBC: RBC is increased.
- In SAH the ratio of WBC: RBC is, however, normal.
- **Normal WBC: RBC is 1 WBC for every 500 – 1000 RBCs.**



Treatment:

- Control blood pressure – to prevent re-bleeding.
- **Calcium channel blocker (nimodipine) – to prevent vasospasm & subsequent stroke:**
 - 30 – 60 mg IV x 5 – 14 days, then:
 - 360 mg PO x 7 days.
- Seizure prophylaxis using phenytoin.
- Surgical clipping of aneurysm.
- Insertion of platinum coil into an aneurysm via an endovascular procedure.
 - Coiling is associated with fewer complications than surgical clipping.
 - Coiling is now the procedure of first choice.

Complications:

- Obstructive hydrocephalus – treated with surgical shunt.
- Delayed cerebral ischemia – treated with vasodilators
- Hyponatremia – treated with water restriction
- Systemic complications:
 - Chest infections
 - Venous thrombosis



CT scan = Ischemic Stroke CT scan = Hemorrhagic Stroke



CT scan = Subarachnoid Hemorrhage

Seizure & Epilepsy

I. Introduction:

▪ Definitions:

- "Seizure" = abnormal, paroxysmal, excessive discharge of CNS neurons.
- "Epilepsy" = recurrent, unprovoked seizures due to a chronic underlying process.

▪ Epidemiology:

- A single seizure is not epilepsy, but an indication for investigation.
- Medication should generally be withheld until recurrent seizures occur.
- The recurrence rate after a first seizure is about 70%.
- The prevalence of epilepsy in developing countries is up to 5 times higher than in developed countries.
- Neurotransmitters:
 - Inhibitory neurotransmitter gamma-aminobutyric acid (GABA) prevents seizure
 - Excitatory neurotransmitters such as acetylcholine, glutamate, and aspartate provoke seizures.

▪ Causes: (mnemonic: VITAMIN-G)

- Vascular (stroke, arteriovenous malformations)
- Infection (meningitis, encephalitis, abscess)
- Trauma
- Autoimmune
- Metabolic (hyponatremia, hypoglycemia, hypocalcemia, hypoxia)
- Idiopathic
- Neoplasm
- Genetic & developmental

▪ Trigger Factors for Seizures:

- Sleep deprivation
- Alcohol (particularly alcohol withdrawal)
- Flickering lights (e.g. TV and computer screens)
- Intercurrent infections
- Loud noises, music
- Hot baths

II. Classification:

- Seizures can be broadly classified into:
 - Partial seizures = arise from discrete, focal portion of brain (one part of cortex)
 - Complex seizures = arise diffusely from both cerebral hemispheres simultaneously

(i). Partial Seizures:

- **Simple Partial Seizure:**
 - It is partial seizure in which there is NO altered level of consciousness.
 - It may be motor, sensory, or autonomic.
 - No automatism,
 - No post-ictal confusion
 - Example:
 - **Jacksonian Seizure:**
 - It is a focal motor seizure.
 - It begins as jerking on one side of mouth or in one hand, sometimes spreading to involve the entire side.
 - **Todd's palsy:**
 - It refers to paralysis of the involved limb after a seizure, with complete recovery within 24 hours.
- **Complex Partial Seizure:**
 - It is partial seizure in which there is altered level of consciousness.
 - No loss of postural tone (i.e. the patient doesn't collapse to the ground)
 - Automatism (blinking repetitively, smacking of lips)
 - Post-ictal confusion
 - Temporal lobe seizures can cause:
 - "Jamais vu" i.e. feelings of unreality
 - "Déjà vu" i.e. undue familiarity
- **Partial Seizure with Secondary Generalization:**
 - It occurs when a partial seizure progresses to a generalized seizure.
 - It typically begins focally and become generalized as the seizure activity involves both cerebral hemispheres.
- **Treatment:**
 - Best initial treatment is monotherapy with first-line agents, such as carbamazepine.
 - In children, phenobarbital is the first-line anti-convulsant.

(ii). Complex Seizures:

▪ Generalized Tonic-Clonic Seizure (Grand-Mal):

- It is complex seizure in which there is loss of consciousness with loss of postural tone.
- Tonic phase is characterized by:
 - Rigidity, loss of consciousness and loss of postural tone.
 - Central cyanosis and eyes roll back.
- Clonic phase is characterized by:
 - Rhythmic contraction alternating with relaxation of all muscle groups.
 - Tongue-biting; urinary and fecal incontinence
- Post-ictal Phase:
 - Confusion and headache,
 - Patients is frightened and wants to sleep
- Management:
 - Diagnosis:
 - Clinical history
 - Electroencephalogram (EEG):
 - 10 Hz activity during tonic phase
 - Slow waves during clonic phase
 - Treatment:
 - Protect the airway.
 - Monotherapy with first – line agents (sodium valproate)

▪ Absence Seizure (Petit Mal):

- It is complex seizure in which there is loss of consciousness but no loss of postural tone.
- It always starts in childhood.
- Brief (5–10 seconds) impaired consciousness occurs up to 20-30 times times/day
- No post-ictal confusion
- Patients are amnesic during and immediately after seizures.
- Patients may appear to be **daydreaming or staring.**
- Diagnosis:
 - EEG:
 - **3 per second spike-and-wave electrical activity.**
 - Hyperventilation can trigger these seizures.
- Treatment:
 - First-line agent = ethosuximide
 - Second-line agent = valproic acid

▪ **Other Forms of Complex Seizures:**

- Atonic Seizure = sudden loss of postural tone lasting 1 – 2 seconds.
- Myoclonic Seizure:
 - Characterized by sudden, brief muscle contractions seen in:
 - Infantile spasms (West syndrome)
 - Juvenile myoclonic epilepsy

III. Investigations:

- Confirm the Diagnosis:
 - EEG:
 - Ambulatory EEG; Standard EEG
 - Sleep EEG; Videotelemetry
- Cause of epilepsy:
 - Structural lesion:
 - MRI
 - CT scan
 - Metabolic Disorder:
 - Urea and electrolytes, blood glucose
 - LFTs, serum calcium, magnesium
 - Inflammatory or infective disorder:
 - CBC, ESR, CRP
 - Chest x-ray, serology for syphilis, HIV
 - CSF examination



Clinical Pearl:

Indication for Brain Imaging (CT/MRI) in Epilepsy:

1. Epilepsy starting after the age of 20 years.
2. Seizures having focal features clinically
3. EEG showing a focal seizure source
4. Control of seizure is difficult or deteriorating

III. Anti-convulsant Pharmacotherapy:

Guidelines for Choice of Anti-epileptic Drugs			
Epilepsy Type	Preferred 1 st – Line Agent	Other 1 st Line Agents	2 nd Line Agent
Partial Seizure and partial seizure with secondary generalization	Carbamazepine	Lamotrigine Sodium valproate Topiramate	Phenytoin Phenobarbital Gabapentin
Primary generalized tonic-clonic seizure	Sodium valproate	Lamotrigine Topiramate	Carbamazepine Phenytoin
Absence Seizure	Ethosuximide	Sodium valproate	Lamotrigine
Myoclonic	Sodium valproate	Clonazepam	Priacetam

(i). Guidelines for Starting Anti-epileptic Drugs:

- Start with one first-line drug.
- Start at a low dose; gradually increase the dose until seizure is controlled.
- Optimize compliance (use minimum number of doses per day)
- If first drug fails, start second first line drug, whilst gradually withdrawing first.
- If second drug fails, start second-line drug in combination with preferred first-line drug at maximum tolerated dose.
- If this combination fails, replace second-line drug with alternative second-line drug.
- If this combination fails, check compliance and re-consider diagnosis.

(ii). Withdrawing Anti-epileptic Drugs:

- After complete control of seizures for > 2 years withdrawal of medication may be considered.
- Classic absence seizures carry the best prognosis for successful drug withdrawal.
- Overall, the recurrence rate of seizures after drug withdrawal is about 40%.
- The EEG is generally a poor predictor of seizure recurrence.
- Withdrawal should be undertaken slowly, reducing the drug dose gradually over 6 – 12 months.

(iii). Drug Side-effects:

<u>Drugs</u>	<u>Average Daily Dose</u>	<u>Side-Effects</u>
Carbamazepine	400 – 1600 mg	<ul style="list-style-type: none"> ○ Aplastic anemia, Leucopenia, Rash ○ Hepatotoxicity, Hyponatremia (SIADH) ○ Toxic epidermal Necrolysis ○ CNS – diplopia, confusion, ataxia
Phenytoin	200 – 400 mg	<ul style="list-style-type: none"> ○ Gum hypertrophy, hypertrichosis, ○ Osteomalacia, folate deficiency ○ Blood dyscrasias, SLE-like syndrome
Valproic Acid (Na valproate)	500 – 2500 mg	<ul style="list-style-type: none"> ○ Hepatotoxicity, increased weight ○ Hair loss, Tremor ○ Menstrual irregularities, polycystic ovarian syndrome
Ethosuximide	500 – 1500 mg	<ul style="list-style-type: none"> ○ Bone marrow suppression ○ Rash, Behavioral changes
Gabapentin	900 – 3600 mg	<ul style="list-style-type: none"> ○ GI upset, Weight gain ○ Nystagmus, Ataxia
Lamotrigine	100 – 300 mg	<ul style="list-style-type: none"> ○ Tremor, Blurred Vision, Insomnia ○ Rash (Stevens Johnson syndrome)

**Clinical Pearl:****Pregnancy & Epilepsy:**

- Seizures often become more frequent during pregnancy, particularly during 3rd trimester.
- With the exception of GABAPENTIN, all anti-convulsant drugs are associated with an increased incidence of fetal congenital abnormalities.
- The risk of complications is greatest when treatment is given during 1st trimester.

IV. Status Epilepticus:

- Definition:
 - It refers to continuous tonic-clonic seizures ≥ 30 minutes – OR:
 - It refers to repeated seizures without resolution of post-ictal encephalopathy



Treatment:

- It is a life-threatening emergency.
- Place patient in semi-prone position to decrease risk of aspiration.
- Ensure airway is patent (oral airway, if prolonged, endotracheal intubation)
- Intravenous access, start normal saline infusion
- Draw blood for CBC, UCE, serum calcium, glucose, serum & urine toxicology screen
- Start:
 - Thiamine (100 mg IV) before dextrose – to prevent Wernicke's encephalopathy
 - Dextrose (50 g IV push)
 - **IV diazepam 10 mg (or IV lorazepam 4mg)**
 - Repeat once only after 15 minutes.
- If seizures continues (after 30 minutes):
 - **IV phenytoin** (1 – 1.5 g IV over 20 minutes) – OR:
 - **IV fosphenytoin** (1 – 1.5 g IV over 10 minutes + 500 mg IV if still seizing)
- If seizures continues (after 30 – 60 minutes):
 - Consider endotracheal intubation
 - EEG monitoring
 - ICU admission
 - **IV phenobarbital** (1–1.5 g IV over 30 minutes + 500 mg IV if still seizing)
 - If still seizing (> 60 minutes) – **General anesthesia** (propofol, midazolam)
- Once seizure is controlled:
 - Long-term anticonvulsant therapy (sodium valproate, or phenytoin)
 - Investigation of cause

Seizure Vs Syncope

Feature	Seizure	Syncope
Aura	Unusual behavior Automatism	Diaphoresis, nausea Tunnel vision
Convulsions	Variable duration	Short duration (< 10 sec)
Post-Ictal State (confusion)	Yes, can be ≥ 30 minutes	None
Associated with	Tongue biting, incontinence	Skin pallor, clamminess

Headache Syndromes

I. Tension Headache:

- It is the most common type of headache.
- **Clinical Features:**
 - The pain is constant and generalized (bilateral).
 - The pain is described as tight, band-like, or like a pressure.
 - The pain aggravates as the day goes on.
 - Triggers – stress, sleep deprivation, dehydration, hunger.
 - In contrast to migraine, tension headache is characterized by:
 - Pain that may continue for weeks to months without interruption.
 - Pain not associated with nausea, vomiting, or aura.

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Treatment:

- Physiotherapy (muscle relaxation and stress management)
- NSAIDs and acetaminophen are first-line abortive therapy.
- Tricyclic anti-depressants (TCA) – low-dose amitriptyline for chronic headache.
- Excessive use of analgesics may actually worsen the headache (“analgesic headache”).

II. Migraine:

- It affects females (20%) more than males (6%).
- It presents before the age of 40 years.
- **Pathogenesis:**
 - It is incompletely understood.
 - Extracranial vessels become distended and pulsatile during a migraine attack.
 - **Cortical Spreading Depression (CSD) Theory of Leao:**
 - It explains the mechanism of migraine with aura.
 - CSD is a well-defined wave of neuronal excitation in the cortical gray matter that spreads from its site of origin at the rate of 2-6 mm/min.
 - This cellular depolarization is responsible for the “aura phase”, which in turn, activates trigeminal fibers, causing the “headache phase”.
- **Clinical Features:**
 - Headache is throbbing (pulsatile), with moderate-to-severe pain.
 - It lasts 4 – 72 hours.
 - It is aggravated with movement & physical activity.

- It is usually relieved by sleep and darkness.
- **Associated with nausea, vomiting, photophobia, & phonophobia.**
- Trigger Factors:
 - Menstruation, Oral contraceptives
 - Cheese, chocolate, red wine

▪ **Types:**

(i). **Migraine without Aura:**

- Also known as "common migraine" – 80%
- Headache (often bilateral), nausea, vomiting, without aura

(ii). **Migraine with Aura:**

- Also known as "Classic Migraine" – 20%.
- Headache (often unilateral), nausea, vomiting, preceded by visual aura:
 - Aura are visual (most common), sensory, motor, or combination of these.
 - Aura develops over 5 – 20 minutes, lasts < 60 minutes.
 - Visual Aura:
 - Scotoma with jagged or colored edge
 - Shimmering, silvery zigzag lines across visual fields

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Treatment:

- Avoid known triggers.
- Abortive therapy:
 - Aspirin, Paracetamol, NSAIDs
 - Severe attacks:
 - Triptans (Sumatriptan) – 5-HT₁ (serotonin) agonists.
 - Triptans are potent vasoconstrictors of the extracranial arteries.
 - Triptans + NSAIDs is stronger than either used alone.
 - Routes – PO, SC injection
 - Contraindications – coronary artery disease, prior stroke
 - Alternatives – Ergotamine
- Preventive Therapy:
 - Indicated if attacks are frequent (> 3 – 4 attacks per month).
 - Agents:
 - Beta blockers
 - Calcium channel blockers
 - Anti-convulsants – valproate, topiramate, gabapentin
 - Tricyclic anti-depressants – amitriptyline

III. Cluster Headache:

- Also known as “**Migrainous Neuralgia**”.
- It is 10 – 15 times less common than migraine.
- It is more common in males (5: 1 ratio) presenting between 20 – 30 years.
- **Pathogenesis:**
 - The cause is unclear.
 - There is little evidence for a genetic predisposition.
 - There are no provoking dietary factors.
 - Imaging studies have suggested abnormal neuronal activity in the hypothalamus.
 - Patients are usually heavy smokers with a higher than average alcohol consumption.
- **Clinical Features:**
 - **Sudden onset severe unilateral headache, lasting 30 – 90 minutes.**
 - Associated with ipsilateral periorbital pain with autonomic features such as:
 - **Ipsilateral lacrimation, nasal congestion, conjunctival injection**
 - Features of Horner’s syndrome (ptosis, miosis)
 - Headaches tend to occur in clusters:
 - Affecting the same part of the head.
 - At the same time of day (commonly in the early hours of morning)
 - And in a certain season of the year.


 Rx

Treatment:

- Abortive Therapy:
 - **Inhalation of 100% oxygen – best abortive therapy – OR:**
 - Subcutaneous injections of Sumatriptan
- Prophylactic Therapy:
 - Migraine prophylactic agents are ineffective in cluster headache.
 - Agents:
 - Calcium channel blockers (verapamil)
 - Oral corticosteroids, **Lithium**, Methysergide,

IV. Pseudotumor Cerebri:

- Also known as “Benign Intracranial Hypertension”.
- **Pathogenesis:**
 - It is caused by a defect in CSF reabsorption by the arachnoid villi.
 - It results in raised intracranial pressure without a space-occupying lesion, ventricular dilatation, or impairment of consciousness.
 - Precipitating Factors:

- Vitamin A (retinoic acid)
- Oral contraceptive pills
- Tetracycline
- **Clinical Features:**
 - It usually occurs in obese young women.
 - **Headache – most common symptom**
 - **It is accompanied by transient diplopia and visual disturbances.**
 - Physical examination:
 - Papilledema
 - 6th (abducent) nerve palsy
- **Diagnosis:**
 - LP = raised CSF pressure, but normal constituents
 - Brain Imaging:
 - CT (or MRI) is required to rule out space occupying lesion.
 - CT is normal, with normal sized ventricles.

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Treatment:

- Avoid precipitating factors.
- **Weight reduction**
- **Acetazolamide (carbonic anhydrase inhibitor) – drug of choice.**
- Repeated lumbar puncture is helpful and mostly unacceptable to patients.
- Surgery – ventriculoperitoneal (VP) shunt

V. Trigeminal Neuralgia (Tic Douloureux):

- It refers to lancinating pain in the 2nd and 3rd divisions of trigeminal nerve (5th cranial nerve)
- It usually occurs in patients over the age of 50 years.
- **Pathogenesis:**
 - The exact mechanism is not clear.
 - It is thought to be caused by vascular compression i.e. an aberrant loop of the cerebellar arteries compressing the trigeminal nerve as it enters the brainstem.
- **Clinical Features:**
 - Severe, repetitive, knife-like pain in the face.
 - Pain can be triggered by:
 - Touching face,
 - Cold wind blowing on the face
 - Eating
 - Pronouncing certain words

R_x**Treatment:**

- Carbamazepine – drug of choice
- Gabapentin – in those who cannot tolerate carbamazepine
- Surgical procedures:
 - Injection of alcohol or phenol into a peripheral branch of the nerve.
 - Surgical decompression of nerve through a posterior craniotomy

**Clinical Pearl:****Headache Warning Signs:**

- Patients with these signs require prompt neuroimaging:
 - Explosive onset (vascular) – SAH
 - Meningism – SAH, Meningitis
 - Positional (lying > standing) – Raised ICP (mass)
 - Nausea & vomiting – Raised ICP (mass), Migraine
 - Visual symptoms – giant cell arteritis, glaucoma, raised ICP
 - Decreased level of consciousness
 - Age > 50 years
 - Immunosuppression

Sleep Disorders

I. Narcolepsy (Gelineau's syndrome):

- It is a sleep disorder with a prevalence of about 1 in 4000.
- **Pathogenesis:**
 - It is associated with HLA-DR2 and HLA-B1.
 - It has familial tendency.
 - It may be caused by deficiency in the hypothalamic hypocretin-containing neurons via autoimmune destruction.
- **Clinical Features:**
 - It occurs in young adults, generally before age 30.
 - **It manifests with excessive daytime somnolence (recurrent bouts of irresistible sleep).**
 - The patient tends to fall asleep when eating, or talking.
 - The periods of sleep are usually short and the person can be woken easily.
 - **The person usually feels refreshed after waking.**
 - EEG shows direct entry into rapid eye movement (REM) sleep.
 - **The Narcolepsy Tetrad:**
 - Sleep Attacks = brief, frequent and unlike normal sleep.
 - Cataplexy = sudden loss of muscle tone set off by surprise, laughter, emotion
 - Sleep paralysis = brief paralysis on waking
 - Hallucination:
 - **"Hypnagogic hallucination"** = occurs as the patient is falling asleep
 - **"Hypnopompic hallucination"** = occurs as the patient awakens

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Treatment:

- Narcoleptic Attacks = CNS stimulants (dexamphetamine, methylphenidate)
- Cataplexy = Clomipramine (TCA), fluoxetine (SSRI)

II. Restless Leg Syndrome:

- Also known as **"Ekbom's syndrome"**.
- It affects up to 2% of population.
- It has strong familial tendency.
- **Clinical Features:**
 - Uncomfortable sensation in the legs that is "creepy and crawly".

- It is present during periods of rest & inactivity.
- It occurs when the patient is tired in the evenings and at the onset of sleep.
- It is aggravated by caffeine and relieved by moving the legs.
- Restless leg can be symptomatic of an underlying condition, such as:
 - Peripheral neuropathy
 - Iron deficiency
 - Uremia

▪ **Treatment:**

- Benzodiazepines (e.g. clonazepam)
- Dopamine agonists (e.g. pramipexole)

Inflammatory Diseases

Multiple Sclerosis (MS):

I. Introduction:

- It is a chronic relapsing-remitting autoimmune demyelinating disorder.
- It is the most common demyelinating disorder.
- It is characterized by destruction of myelin and oligodendrocytes.
- It is multifactorial disease; lifetime risk of developing MS is about 1 in 400.
- It is about twice as common in women as men.
- Risk factors:
 - Female gender
 - Family history
 - Strong association with HLA-DR2
 - Any age (20 – 40 years)
 - Vitamin D.
 - Cold climates
 - Sun-exposure
 - Epstein-Barr Virus (EBV)

II. Pathogenesis:

- Both genetic & environmental factors play important role in pathogenesis.
- Immune Theory of Demyelination:
 - The earliest step in pathogenesis is breakdown of blood brain barrier (BBB).
 - It is initiated by TH1sub-set of CD4 (Helper T) cells.
 - CD4 cells react against Myelin Basic Protein (MBP).
 - These myelin-reactive T-cells express adhesion molecules, allowing their entry through BBB.
 - T-cells are activated by antigen presenting cells (APCs) – macrophages, microglia
 - T-cells then secrete pro-inflammatory cytokines – interferon- γ , tumor necrosis factor- α
 - This results in destruction of myelin, resulting in demyelination.
- Pathology:
 - Pathologic demyelinating lesions of MS are called “**plaques**”.
 - Plaques appear as indurated areas – hence the name “sclerosis”.

III. Clinical Features:

- Sensory Dysfunction:
 - Paresthesias
 - Loss of pain and temperature sensation.
 - Loss of vibration sensation.
- Upper Motor Neuron:
 - Increased deep tendon reflexes.
 - Spasticity, weakness
 - Positive Babinski’s sign.

- Autonomic Dysfunction:
 - Sexual dysfunction
 - Urinary incontinence
 - Bowel motility disorders.
- Unique Features:
 - Bilateral trigeminal neuralgia
 - **Lhermitte's sign** = electrical sensation travelling down the back on neck flexion.
 - **Optic Neuritis**:
 - It is **central visual field defect**. (most common presentation)
 - It presents with sudden loss of vision.
 - **Charcot's Triad (SIN)**:
 - Scanning Speech
 - Intranuclear Ophthalmoplegia (INO)
 - Nystagmus

Clinical Pearl:

Intranuclear Ophthalmoplegia:

- It is also known as MLF-syndrome.
- It refers to demyelination of medial longitudinal fasciculus (MLF) in mid-brain.
- When patient is made to gaze contralaterally (towards unaffected eye) there is:
 1. Weakness in adduction of ipsilateral eye (affected eye),
 2. With abduction and nystagmus of contralateral eye (normal eye).

Clinical Pearl:

Subtypes of MS:

1. Relapsing – Remitting MS:
 - It is characterized by episodes of acute relapses followed by periods of variable recovery.
 - It is the most common type (80%), and carries **best prognosis** (no progression).
2. Primary Progressive MS:
 - It is characterized by progressive disease from the onset, with early onset disability.
 - It has no acute episodes of relapse. Poor prognosis.
3. Secondary Progressive MS:
 - It is a relapsing – remitting disease that is not progressive at the onset.
 - It becomes progressive later in the course, causing disability. Poor prognosis.
4. Fulminant MS:
 - It is characterized by progressive disease from the onset, leading to early death.
 - It has acute episodes of relapses. **Worse prognosis**.

IV. Laboratory Findings:

- CSF Findings:
 - Increased CSF leukocytes = CD4 T-lymphocytes
 - Increased CSF protein = γ -globulins (IgG)
 - Increased myelin basic protein = Sign of active disease
 - CSF glucose = Normal
 - CSF protein = < 100 (if > 100 MS is less likely)
 - CSF electrophoresis = Oligoclonal bands (70-90% between attacks)
- **Oligoclonal Bands:**
 - Discrete bands of protein in gamma globulin region.
 - Sign of demyelination, but NOT specific to MS.
- MRI with gadolinium:
 - It is the **Gold Standard investigation (most sensitive)**.
 - It shows multiple, asymmetric, often peri-ventricular white matter lesions.



MRI = Multiple Sclerosis

V.

R_x**Treatment:****Acute Exacerbations:**

- Pulses of high-dose steroids are given in acute exacerbation.
- Steroid can be given orally or IV over 3 – 5 days.
- Steroids must be in intravenous (not oral) form for treatment of optic neuritis.

Prevention of Disease Progression (Disease Modifying Agents):

- Beta-interferon – reduces relapse rate
- Glatiramer Acetate (copolymer-1)
- Mitoxantrone
- Natalizumab – inhibitor of $\alpha 4$ -integrin.
 - It is somewhat more effective than beta-interferon and Glatiramer.
 - It carries 1: 500 risk for JC virus-mediated progressive multifocal leukoencephalopathy (PML).
- Fingolimod:
 - It is derived from fungal precursor (myriocin).
 - It is the first oral agent approved for MS.

Treatment of Complications:

- Spasticity:
 - Physiotherapy
 - Baclofen (15 – 100mg orally in divided doses); Dantrolene
- Ataxia:
 - Isoniazid
 - Clonazepam
- Bladder Symptoms:
 - Atonic Bladder:
 - It is a feature of lower motor neuron abnormality.
 - It causes bladder distention with overflow; residual urine volume is > 100 ml.
 - Treatment:
 - Intermittent self-catheterization
 - Indwelling catheterization.
 - Hypertonic Bladder:
 - It is a feature of upper motor neuron abnormality.
 - It causes urge incontinence, incomplete bladder emptying; residual urine volume is < 100 ml.
 - Treatment:
 - Anti-cholinergics (oxybutynin, imipramine)
 - Intermittent self-catheterization

VI. Prognosis:

- Good prognosis = optic neuritis with purely sensory relapses.
- Poor prognosis:
 - Late-onset
 - Male gender
 - Frequent relapses with incomplete recovery
 - Motor signs at onset
 - Multiple lesions on MRI

Transverse Myelitis:

I. Introduction:

- It is an acute, inflammatory, demyelinating disorder affecting the spinal cord over a variable number of segments.
- **Clinical Features:**
 - Subacute paraparesis with a sensory level.
 - Severe pain in the neck or back at the onset.
 - **Neuromyelitis Optica (NMO):**
 - Also known as “Devic’s Syndrome”.
 - It refers to transverse myelitis, with bilateral optic neuritis.
 - It is due to antibody against a water channel, “Aquaporin 4”, found in cells near the ventricular system of the brain.
 - Spinal MRI shows lesions which are typically longer than 3 spinal segments (unlike the lesions of MS, which are shorter than this)
- **Risk of Multiple Sclerosis:**
 - Factors associated with increased risk of MS after an attack of transverse myelitis:
 - Severe weakness
 - Catastrophic onset
 - Initial lancinating pain
 - Incontinence
 - **Spinal shock**
 - **Sensory disturbance at cervical level**
 - **Presence of protein 14.3.3 in CSF**

II. Management:

- **Diagnosis:**
 - MRI:
 - It is the investigation of choice.
 - It distinguishes this from spinal cord compression

- CSF:
 - Cellular pleocytosis; often with polymorphs at the onset
 - Oligoclonal bands are usually absent

▪ **Treatment:**

- High-dose intravenous methylprednisolone
- Outcome is variable; patients may develop MS in later years.



Clinical Pearl:

UMN lesion v/s LMN lesion:

- UMN lesions are caused by damage to motor pathways anywhere from motor nerve cells in the pre-central gyrus of the frontal cortex, through the internal capsule, brainstem and cord, to the anterior horn cells in the cord.
- LMN lesions are caused by damage anywhere from anterior horn cells in the cord, nerve roots, plexus, or peripheral nerves.

<u>UMN lesions</u>	<u>LMN lesions</u>
Weakness	Weakness
No atrophy	Atrophy
No fasciculations	Fasciculations
Reflexes = increased	Reflexes = decreased
Tone = increased	Tone = decreased
Babinski's sign = positive	Babinski's sign = negative
Spastic paralysis	Flaccid paralysis
Clasp knife spasticity	No clasp knife spasticity

Dementia

I. Alzheimer's Disease (AD):

- It is the most common cause of dementia in elderly.
- It rarely becomes symptomatic before the age of 50 years.
- It is mostly sporadic, while only 15% of cases are familial.
- It has strong association with Down's syndrome (trisomy 21)
- **Genetics:**
 - It can be divided into two main groups:
 - Early – onset AD = autosomal dominant inheritance
 - Late – onset AD = polygenic inheritance
 - It is associated with mutations in following chromosomes:
 - Chromosome 21 = Gene is amyloid precursor protein (APP).
 - Chromosome 19 = Gene is presenilin-1 (PS1)
 - Chromosome 14 = Gene is presenilin-2 (PS2)
 - Chromosome 1 = Gene is Apolipoprotein E (ApoE).
- **Morphology:**
 - (i). Gross Findings:
 - Diffuse cortical atrophy
 - Enlarged ventricles (Hydrocephalus ex Vacuo)
 - (ii). Microscopic Findings:
 - **Neuritic Plaques:**
 - These are neuronal cell processes around central amyloid ($A\beta$) core.
 - These are formed due to defective degradation of amyloid precursor protein.
 - **Neurofibrillary Tangles:**
 - These are bundles of filaments in the cytoplasm of neurons.
 - These are due to hyper-phosphorylation of tau protein in neuron.
- **Clinical Features:**
 - Gradual onset dementia.
 - **Impairment of the ability to remember new information – key clinical feature.**
 - **Short-term and long-term memory are both affected.**
 - Short term memory is affected more than long-term memory.
 - Anosognosia (patients deny that there is anything wrong with them).
 - Language deficits, apraxia (inability to perform skilled movements)
 - Depression, agitation, and psychosis.
 - Most common cause of death = aspiration pneumonia
- **Treatment:**
 - Cholinesterase inhibitors = donepezil, rivastigmine
 - Glutamate (NMDA receptor) antagonist = memantine

II. Pick's Disease:

- Also known as "**Frontotemporal Dementia**".
- It is progressive form of dementia characterized by atrophy of frontal and temporal lobes.
- **Clinical Features:**
 - **Behavior & personality changes** – early in disease (frontal lobe).
 - **Language disturbances (temporal lobe)**
 - Inattentiveness; compulsive behaviors.
 - Dementia (memory relatively preserved in early stages)
- **Morphology:**
 - Lobar atrophy:
 - Asymmetrical atrophy of frontal and temporal lobe.
 - While Alzheimer's disease has diffuse atrophy of all lobes.
 - **Pick Bodies:**
 - Weakly basophilic, intra-cytoplasmic inclusions.
 - They are inclusion bodies of "Tau" protein, rather than the "Ubiquitin" as in Alzheimer's disease.

III. Lewy Body Dementia:

- It is a progressive, degenerative dementia of unknown etiology.
- **Clinical Features:**
 - Dementia
 - **Visual hallucination**
 - **Parkinsonian motor features**
 - Fluctuating cognition:
 - Periods of being alert, coherent, and oriented.
 - Alternating with periods of confusion and inattentiveness
- **Treatment:**
 - No specific treatment
 - Dopamine agonists (levodopa, carbidopa)
 - Anti-cholinesterase inhibitors (donepezil, rivastigmine)

IV. Vascular Dementia:

- It is the second most common type of dementia.
- It is associated with a history of stroke and cerebrovascular disease.
- **Risk Factors:**
 - Age; Hypertension
 - Diabetes; Stroke

- Multiple emboli
- Amyloid angiopathy

▪ **Clinical Features:**

- Dementia
- Focal neurologic signs on examination
- Onset of symptoms is abrupt, stepwise, or related to stroke.
- Brain Imaging (CT/MRI):
 - Evidence of old infarctions
 - Extensive deep white-matter changes secondary to ischemia

IV. Normal Pressure Hydrocephalus (NPH):

- It is a potentially treatable form of dementia.
- It is thought to arise from impaired CSF outflow from the brain.
- It is characterized by dilatation of the ventricular system by intermittent rises in CSF pressure, which occur particularly at night.
- **Clinical Features:**
 - Old age
 - **Classic Triad of (3 W's):**
 - Dementia (wobbly)
 - Gait apraxia (whacky)
 - Urinary incontinence (wet)
 - Gait is classically described as "magnetic" – "feet glued to the floor".
 - Gait is broad-based and shuffling (Parkinsonism has narrow-based gait).
 - Headache and other signs of raised intra-cranial pressure (ICP), such as papilledema typically do NOT appear.
- **Diagnosis:**
 - LP = normal CSF opening pressure
 - MRI:
 - Ventricular enlargement, out of proportion to sulci atrophy, i.e.:
 - Sulci are normal (while in AD, ventricular enlargement is associated with sulci atrophy)

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Treatment:

- Lumber puncture CSF drainage for several days may improve symptoms.
- If so, surgical CSF shunting is the treatment of choice.

V. Creutzfeldt – Jakob Disease:

- It is the most common prion disease.
- It is a member of the transmissible spongiform encephalopathies, all of which are characterized by spongy degeneration, neuronal loss, and astrocytic proliferation.
- It has no effective treatment.
- **Clinical Features (mnemonic: DAM):**
 - Dementia, which is rapidly progressive.
 - Ataxia
 - Myoclonic jerks
 - It is fatal disease, with an average duration of only 4-6 months.
 - Risk Factors = corneal transplantation, contact with human brain.
- **Diagnosis:**
 - Suggested by clinical features.
 - EEG = repetitive slow-wave complexes
 - **CSF = elevated levels of 14-3-3 and tau protein**
 - Definitive diagnosis = brain biopsy or autopsy

Movement Disorders

Tremors:

- Abnormal movements are often caused by a disorder in the basal ganglia.
- Tremors refer to rhythmic oscillating movement of a limb or part of a limb, or of the head.
- **Resting Tremor:**
 - It is pathognomonic of Parkinson's disease.
 - **It is a tremor that is present at rest, but disappears with action.**
 - It occurs at a frequency of 4 – 8 Hz.
 - It is characteristically "pill-rolling" and usually asymmetrical.
- **Physiological Tremor:**
 - **It is the most common type of action tremor.**
 - It occurs at a frequency of 8 – 12 Hz.
 - It is common in normal subjects, but exaggeration can occur in:
 - Anxiety
 - Thyrotoxicosis; Pheochromocytoma
 - Hypoglycemia; Alcohol withdrawal
 - Drugs (e.g. beta agonists, caffeine, lithium)
- **Essential Tremor:**
 - **It is a tremor that is present both at rest and with intention** (reaching for things).
 - It is often inherited.
 - Alcohol suppresses it, while caffeine makes it worse.
 - Treatment = beta blockers (propranolol)
- **Intention Tremor:**
 - **It is a tremor that is present with intention only, not at rest.**
 - It typically occurs in cerebellar disease.
 - Holmes' Tremor:
 - It is a violent, large-amplitude postural tremor that worsens as a target is reached
 - It is a type of intention tremor that occurs with lesions in superior cerebellar peduncle.
- **Flapping Tremor:**
 - Also known as "Asterixis"; it is typical of metabolic disturbances.
 - It is a tremor that presents with jerking movements of hand when the wrist is extended.

- Causes:
 - Liver failure; Renal failure
 - Hypercapnia
 - Drug toxicity
 - Thalamic lesions
- **Other Movement Disorders:**
 - Chorea = jerky, small-amplitude, purposeless involuntary movements.
 - Athetosis = slow, writhing movement of the limbs.
 - Dystonia = sustained involuntary contraction that causes abnormal posture or movement
 - Myoclonus = brief, isolated, random, non-purposeful jerks of muscle groups in limbs.
 - Tics:
 - Repetitive, semi-purposeful movements such as blinking, winking, grinning.
 - Patient has the ability to suppress their occurrence, at least for a short time.

Parkinsonism:

I. Introduction:

- It is a group of disorders that alter dopaminergic pathways involved in voluntary muscle movement.
- Striatal system is involved in voluntary muscle movement.
- Striatal system consists of substantia nigra, caudate, putamen, globus pallidus, and thalamus.
- Dopamine is the principal neurotransmitter in the nigrostriatal tract.
- Nigrostriatal tract connects substantia nigra with the caudate and putamen.
- **Causes:**
 - Parkinson disease (PD)
 - Corticobasal degeneration (CBD)
 - Wilson's disease
 - MPTP (meperidine derivative)
 - Chronic carbon monoxide poisoning – due to necrosis of globus pallidus.
 - Anti-psychotic drugs – e.g. phenothiazine

II. Parkinson's disease:

- It is an idiopathic hypokinetic disorder that presents with signs and symptoms of Parkinsonism.

- It is due to degeneration of neurons in substantia nigra resulting in deficiency of dopamine.
- **Clinical Features:**
 - Resting tremor:
 - Pathognomonic feature; it is "pill rolling".
 - It occurs at a frequency of 4 – 6 Hz.
 - Postural Tremor:
 - It is less obvious, faster, and finer than resting tremor.
 - It occurs at a frequency of 8 – 10 Hz.
 - Rigidity:
 - Cogwheel rigidity – mostly upper limbs
 - Plastic (lead-pipe) rigidity – mostly lower limbs.
 - Bradykinesia – slowness of movements.
 - Festinating gait – a wide leg stance with short accelerating steps i.e. a narrow-based gait.
 - Postural instability – stooped posture.
 - Reduced arm swing
 - Impaired balance on turning
 - Expressionless face (masklike) – ("hypomimia")
 - Small handwriting ("micrographia")
 - Although the features are initially unilateral, gradual bilateral involvement is the rule.
- **Morphology:**
 - Pallor of substantia nigra.
 - Loss of pigmented catecholaminergic neurons.
 - **Lewy bodies= intracytoplasmic, eosinophilic inclusions**

III.

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Treatment:

- **Indications:**
 - PD severe enough to affect activities of daily living.
 - First-line Agents:
 - Carbidopa-Levodopa – OR:
 - Non-ergot derived dopamine agonists – OR:
 - Monoamine oxidase inhibitors (MAO-inhibitors)
- **Carbidopa – Levodopa:**
 - **This combination therapy is the mainstay of treatment.**
 - This combination is particularly effective at improving bradykinesia and rigidity.
 - Levodopa is dopamine pro-drug, while Carbidopa is dopa-decarboxylase inhibitor.

- If levodopa is administered orally, more than 90% is decarboxylated to dopamine peripherally, and only a small portion reaches the brain.
- This peripheral conversion of levodopa is minimized by decarboxylase inhibitor that does not cross blood brain barrier along with levodopa.
- Side Effects:
 - Postural hypotension
 - Nausea and vomiting
 - Orofacial dyskinesias
 - Limb and axial dystonia
 - Personality changes with increased gambling, and hyper-sexuality
 - On & Off Phenomenon:
 - "ON" – characterized by bradykinesia due to insufficient dopamine.
 - "OFF" – characterized by dyskinesia due to excess dopamine

▪ **Other Treatment Options:**

- Dopamine Agonists:
 - Dopamine agonists are less effective than levodopa, with more side-effects.
 - Non-ergot derivatives (ropinirole, pramipexole) preferred over ergot-derived (bromocriptine, cabergoline).
- Monoamine oxidase (MAO-B) Inhibitor:
 - This enzyme is involved in breakdown of excess dopamine in the synapse.
 - Agents – selegiline, rasagiline.
- Catechol-O-methyltransferase (COMT) Inhibitors:
 - This enzyme is involved in peripheral breakdown of levodopa.
 - Agents – entacapone, tolcapone.
 - These agents extend the duration of levodopa.
 - Tolcapone is associated with hepatotoxicity.
- Anti-Cholinergics:
 - Agents -- benztropine, trihexyphenidyl
 - These agents are effective in relieving tremor & rigidity.
 - Side-effects:
 - Dry mouth, Constipation
 - Blurred vision, Urinary retention, Confusion
- Amantadine:
 - Atypical dopamine agonist
 - Side effects = livedo reticularis, peripheral edema, confusion, seizures
- Surgical Options:
 - Deep brain stimulation (DBS) of thalamus – for tremors
 - DBS of globus pallidus, subthalamic nucleus
 - DBS is reserved for medically refractory cases.



Clinical Pearl: **Parkinsonian Syndromes:**

Lewy Body Dementia:

- It is Parkinsonism + Dementia.
- It presents with:
 1. Dementia
 2. Visual hallucination
 3. Impaired visuo-spatial abilities
 4. And features of parkinsonism

Multiple System Atrophy (MSA):

- Characterized by α -synuclein cytoplasmic inclusions in basal ganglia, cerebellum, & motor cortex.
- Prognosis poor than Parkinson disease.
- Cognition is preserved.
- It has following subtypes:
 - "MSA-P" – MSA with predominant parkinsonian features
 - "MSA-C" – MSA with cerebellar ataxia
 - "Shy – Dragger Syndrome":
 - Parkinsonism + Autonomic Dysfunction
 - Autonomic dysfunction – ataxia, orthostatic hypotension

Corticobasal Degeneration (CBD):

- Characterized by widespread tau-protein deposition throughout brain.
- Features:
 - Parkinsonism, Dystonia, Myoclonus
 - "Alien Hand Phenomenon" – hand movement without conscious control.

Huntington's disease (HD):

- It is a hyperkinetic autosomal dominant disease.
- It is a trinucleotide repeat disorder (CAG) involving chromosome 4.
- It is pathologically characterized by degeneration of GABA-nergic neurons of caudate nucleus.
- It is a relentlessly progressive with an average course of about 15 years to death.
- **Clinical features:**
 - Begins in the middle adult life.
 - **Mnemonic: 3 M's**
 - Movement – chorea (sudden purposeless, involuntary dancelike movements)

- Memory – dementia
- Mood
 - Changes in personality (irritability, moodiness)
 - Suicidal tendency; anti-social behavior
- **Westphal Variant HD:**
 - It is juvenile-onset Huntington's disease.
 - It presents with parkinsonian features with rigidity.
- **Diagnosis:**
 - Diagnosis is made clinically.
 - Supported by CT or MRI finding of striking atrophy of caudate nucleus.
- **Management:**
 - Treatment is symptomatic:
 - Dyskinesia = tetrabenazine
 - Depression = SSRI (e.g. fluoxetine)
 - Psychosis = haloperidol
 - Genetic counseling should be offered to offspring



Clinical Pearl:

Huntington's Disease:

- HD shows phenomenon of "Anticipation".
- Anticipation means earlier expression and more severe disease in subsequent generations.

Miscellaneous Degenerative Conditions

I. Motor Neuron Disease (MND):

- Also known as “Lou Gehrig’s disease”.
- It is a chronic, progressive neurodegenerative disease of unknown etiology.
- It is characterized by degeneration of motor neurons in the cerebral cortex, cranial nerve nuclei and anterior horn cells of spinal cord.
- **Features:**
 - Males > females
 - Age = between 40 and 60 years.
 - The prevalence of disease is about 5: 100,000
 - Familial cases (5-10%) are due to mutations of copper-zinc superoxide dismutase gene (SOD1) on chromosome 21.
 - Mean time from diagnosis to death = 50% die within 2 year of diagnosis.
 - **Most common cause of death = respiratory infection and failure**

▪ **Clinical Features:**

- It is most commonly characterized by a combination of UMN & LMN signs.
- Signs of Upper Motor Neuron (UMN) disease:
 - Hyper-reflexia
 - Spasticity
 - Babinski’s Sign
- Signs of Lower Motor Neuron (LMN) disease:
 - Muscle weakness & wasting
 - Fasciculations and flaccid paralysis
 - Disease is called “**progressive muscular atrophy**” if LMN signs predominate.
- Other Features:
 - Emotional lability is a common feature.
 - Eye movements are spared – (unlike myasthenia gravis)
 - Sphincter tone is spared – (unlike multiple sclerosis)
 - Difficulty in chewing, swallowing, and weight loss.

▪ **Disease Patterns (3 Patterns):**

(i). Amyotrophic Lateral Sclerosis (ALS):

- It is the most common pattern of motor neuron disease (50%).
- UMN features = hyper-reflexia, spasticity, extensor plantar (+ve Babinski’s sign)
- LMN feature = muscle weakness, fasciculation, and wasting

(ii). Progressive Muscular Atrophy:

- It predominantly affects spinal motor neurons; therefore **presents with LMN signs.**

- LMN features = muscle weakness, fasciculation, wasting, absent reflexes.
- (iii). Progressive Bulbar Palsy:
 - In this pattern there is involvement of nuclei of cranial nerves IX – XII in medulla.
 - **It presents with LMN signs** of tongue and muscles of talking & swallowing.
 - Tongue = wasting, fasciculation, and flaccid
 - Jaw jerk = normal
 - Speech = quiet, hoarse, nasal
- **Treatment:**
 - Riluzole:
 - It is glutamate antagonist
 - It slows the progression of disease.
 - Palliative Care:
 - Non-invasive ventilatory support
 - Feeding support – percutaneous gastrostomy
 - Speech & occupational therapists
 - Physiotherapy

<u>Bulbar Palsy</u>	<u>Pseudobulbar Palsy</u>
"Definition" = It refers to bilateral lower motor neuron (LMN) disease involving CN-IX, X, XI, and XII.	"Definition" = It refers to bilateral upper motor neuron (UMN) disease involving CN-IX, X, XI, and XII.
"Speech" = dysarthria	"Speech" = dysarthria, dysphonia
"Swallowing" = dysphagia	"Swallowing" = dysphagia
"Tongue" = weakness, wasting, fasciculations	"Tongue" = spastic, slow moving
"Jaw jerk" = absent	"Jaw jerk" = increased
"Pharyngeal & palatal reflexes" = decreased	"Pharyngeal & palatal reflexes" = increased
"Emotional lability" = absent	"Emotional lability" = present (e.g. weeping unprovoked by sorrow)
"Causes" = motor neuron disease, Guillain-Barre syndrome, poliomyelitis, Lyme disease, myasthenia gravis	"Causes" = multiple sclerosis, stroke, central pontine myelinolysis, progressive supranuclear palsy

II. Friedreich's Ataxia:

- Trait = autosomal recessive.
- Chromosome = 9
- It is caused by GAA trinucleotide repeated expansion in the first intron of a gene encoding a protein called "frataxin".

▪ **Clinical Features:**

- Onset = first decade of life
- Gait ataxia
- Hand clumsiness and dysarthria
- Absent deep tendon reflexes
- Loss of joint position and vibratory sensation
- Hypertrophic cardiomyopathy
- Type-I diabetes – 10%
- Patient is wheelchair bound within 5 years of onset
- Cause of death – pulmonary infection and cardiac disease

III. Wernicke – Korsakoff Disease:

- It is caused by deficiency of vitamin B1 (thiamine), which is caused by:
 - Alcoholism – most common
 - Malnutrition
 - Malabsorption
 - Protracted vomiting (e.g. hyperemesis gravidarum)

▪ **Clinical Features:**

- Acute confusional state (Wernicke's encephalopathy)
- Ataxia, nystagmus, and extraocular muscle weakness.
- **Korsakoff syndrome:**
 - It occurs if Wernicke's encephalopathy is inadequately treated.
 - It presents with profound disturbance of short-term memory associated with a tendency to confabulate.

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Treatment:

- It should be considered and treated in any confused or demented patient.
- Thiamine replacement:
 - Intravenously 2 vials 8-hourly for two days; followed by
 - Oral thiamine (100 mg 8-hourly)
 - Treat the underlying cause

Clinical Pearl:

Confabulation:

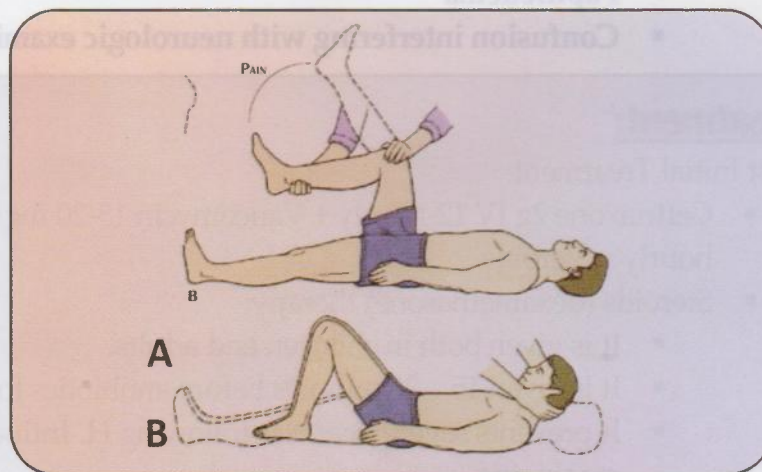
- It refers to plausible, but false memories, in an attempt to cover memory gaps (unconsciously fabricated facts).
- It is a core feature of Korsakoff's syndrome, a complication of chronic alcoholism (thiamine deficiency).

CNS Infections

Meningitis:

I. Acute Pyogenic Meningitis:

- It refers to acute bacterial inflammation of the leptomeninges and CSF within subarachnoid space.
- **Causes:**
 - Overall = Streptococcus pneumoniae
 - Neonates = E. coli and group B streptococci (streptococcus agalactiae).
 - Adults = Neisseria meningitides (most common), S. pneumoniae
 - Elderly = Streptococcus pneumoniae and Listeria monocytogenes
- **Symptoms:**
 - High grade fever
 - Headache, neck stiffness, photophobia
 - Altered consciousness
 - Nausea and vomiting
 - Seizures
- **Signs:**
 - Nuchal rigidity
 - **Brudzinski's Sign:**
 - Support the patient's head with the fingers of your hands at the occiput.
 - Flex the patient's head gently until the chin touches the chest.
 - Positive Brudzinski's sign:
 - It is reflex (involuntary) flexion of knees, in response to neck flexion
 - The patient assumes a "fetal position".



A = Kernig's Sign
B = Brudzinski's Sign

○ **Kernig's Sign:**

- The patient lies supine.
- Flex one of the patient's leg at the hip & the knee, with your left hand
- Use your right hand to extend the KNEE only.
- Positive Kernig's sign:
 - Pain (due to resistance) on knee extension (by the spasm of the hamstrings).
 - The other leg may flex at the KNEE & the HIP.

○ **Other Possible Signs:**

- Focal neurologic findings = hemiparesis, visual field defects, cranial nerve palsies
- Fundoscopic findings = papilledema, absent venous pulsations
- Rash = maculopapular, petechial, or purpuric (purpuric rash is seen in 70% of meningococcal meningitis)

▪ **Diagnosis:**

- Blood cultures before starting antibiotics.
- **Best initial test = lumbar puncture (LP)**
- **Most accurate test = lumbar puncture**
- CT scan:
 - CT scan of head is necessary BEFORE lumbar puncture if there is possibility that a space occupying lesion may cause herniation (i.e. coning).
 - CT scan of head however should NOT delay antibiotic treatment of presumptive meningitis.
 - Indications of CT scan BEFORE lumbar puncture are:
 - **Focal neurologic abnormalities**
 - **Seizures**
 - **Papilledema**
 - **Confusion interfering with neurologic examination**

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Treatment:

- **Best Initial Treatment:**
 - Ceftriaxone 2g IV 12-hourly + Vancomycin 15-20 mg/kg IV 12-hourly + Steroids
 - Steroids (dexamethasone) therapy:
 - It is given both in children and adults.
 - It is given 15 – 20 minutes before antibiotics for 2 – 4 days.
 - It prevents severe deafness following H. Influenzae type B meningitis

- Other Regimens:
 - (i). Patient with a typical meningococcal rash:
 - Benzyl penicillin 2.4 g IV 6-hourly.
 - (ii). Patient with clear history of anaphylaxis to beta-lactam drugs:
 - Chloramphenicol plus vancomycin
 - (iii). *Listeria Monocytogenes*:
 - It is resistant to all cephalosporins, but sensitive to penicillin.
 - **Add ampicillin** to ceftriaxone and vancomycin.
 - Risk factors:
 - Elderly (all those > 50 years age)
 - Neonates
 - AIDS & HIV
 - Immunocompromised
 - Pregnancy

▪ **Complications:**

- Deafness (CN VIII palsy) – most common
- Cerebral edema
- Communicating & non-communicating hydrocephalus
- Ventriculitis (inflammation of the ventricles seen in fulminant cases)
- Hyponatremia
- Subdural empyema

▪ **Prevention of Meningococcal Infection:**

- Indication for Prophylaxis:
 - Household contacts – during the 7 days prior to disease onset
 - Child-care & nursery school contacts
 - Aircraft contacts for persons seated next to the patient for > 8 hours
 - Contact with patient's oral secretions – during 7 days prior to disease onset
 - Kissing
 - Sharing of toothbrushes
 - Sharing of eating utensils
 - Mouth-to-Mouth resuscitation
 - Endotracheal intubation
- Children = oral rifampicin for two days:
 - Age 3 – 12 months = 5 mg/kg 12-hourly
 - Age > 1 year = 10 mg/kg 12-hourly
- Adults:
 - Rifampicin, OR
 - Single dose of 500 mg ciprofloxacin

- Meningococcal Vaccines:
 - They are for prevention of disease caused by meningococci of groups A and C.
 - They are not useful for group B, which is the most common serogroup.

II. Tuberculous Meningitis:

- It is caused by Mycobacterium tuberculosis.
- It results from complication of primary tuberculosis.
- Most common site: base of the brain.
- **Clinical Features:**
 - Symptoms:
 - Headache and low-grade fever,
 - Vomiting
 - Lassitude, depression,
 - Confusion and behavioral changes
 - Signs:
 - Signs of meningism (headache, photophobia, and neck rigidity) may be absent.
 - Oculomotor palsies
 - Papilledema
 - Focal neurologic signs
- Treatment:
 - Anti-tuberculous therapy (ATT) + steroids
 - Steroid decreases mortality, but not focal neurologic damage.

III. CSF Findings in Meningitis:

CSF	Bacterial	Viral	Tuberculous
Pressure (9–18 cm H ₂ O)	Increased	Normal	Increased
Appearance	Cloudy	Clear	Cloudy
White cell count (< 5 cells/mm ³)	1000 – 20,000	10 – 2000 cells/mm ³	50 – 5000 cells/mm ³
Differential count	Polymorphs (neutrophils)	Mononuclear (lymphocytes)	Mixed; initially polymorphs, then mononuclear
Glucose (50 – 75 mg/dL)	Decreased (markedly)	Normal	Decreased
Protein (15 – 45 mg/dL)	Increased	Increased	Increased (markedly)
Gram Stain	Positive 60 – 90% Culture positive 60– 90%	Negative	Negative

Viral Encephalitis:

I. Introduction:

- It refers to viral infection of brain parenchyma with evidence of neurologic dysfunction.
- **Etiologies:**
 - Herpes simplex virus (HSV):
 - Most common cause
 - Most commonly involve the temporal lobes
 - Cytomegalovirus (CMV) – most commonly involves areas adjacent the ventricles.
 - Varicella-Zoster virus (VZV)
 - Arboviruses
 - Enteroviruses (e.g. Coxsackie)
- **Clinical Features:**
 - Acute onset of headache,
 - Fever, focal neurologic signs (aphasia, hemiplegia), and seizures
 - Altered level of consciousness ranging from drowsiness to deep coma.
 - Meningism occurs in many patients.

II. Management:

- **Diagnosis:**
 - Best initial test = CT scan (because of presence of confusion)
 - Lumbar Puncture:
 - Cells = lymphocytes
 - Protein = raised
 - Glucose = normal
 - RBCs = present
 - **The presence of RBCs in CSF without a history of trauma is highly suggestive of HSV-encephalitis.**
 - PCR of CSF is the most accurate for HSV – encephalitis, and CMV, VZV, and Enteroviruses.
 - MRI = characteristic temporal lobe abnormalities in HSV encephalitis
 - EEG = to rule out seizure, findings in encephalitis are non-specific.
- **Treatment:**
 - Anti – convulsant therapy.
 - Dexamethasone (8mg 12-hourly) for raised intracranial pressure
 - HSV and VZV = intravenous acyclovir
 - CMV = ganciclovir with or without foscarnet.
 - Supportive care for other etiologies

Brain Abscess:

I. Introduction:

- It refers to focal suppurative infection of the brain parenchyma.
- It most commonly affects the frontal lobe, followed by parietal lobe.
- **Agents:**
 - Streptococci – overall most common agent
 - Staphylococcus– most common agent in penetrating injuries
 - Anaerobes
 - Polymicrobial (multiple organisms in 80 – 90% cases)
- **Source of Infection:**
 - Penetrating injury
 - Mastoiditis; Sinusitis
 - Acute bacterial endocarditis
 - Bronchiectasis
 - Cyanotic congenital heart disease.
- **Clinical Features:**
 - Headache, most common feature. It is dull and constant.
 - Focal neurologic deficits and seizures
 - Signs of raised intracranial pressure.
 - CN III and CN VI palsy.
 - CT scan = **ring-enhancing lesion** with a low-density core.

II. Management:

- **Diagnosis:**
 - CT scan:
 - **It is the best initial test.** (lumber puncture should never be performed first)
 - It show ring-enhancing lesion with a low-density core.
 - Lumber puncture is not necessary and may precipitate brainstem herniation.
 - Lab findings:
 - Increased WBCs
 - Elevated ESR and CRP

R_x**Treatment:**

- Antibiotics:
 - Initiate broad-spectrum IV antibiotics e.g.
 - Ceftriaxone + metronidazole ± vancomycin IV for 6 – 8 weeks
- Other Measures:
 - Anti-convulsant agents.
 - Dexamethasone in severe cases to decrease cerebral edema.
 - IV mannitol to decrease intracranial pressure.
 - Surgical drainage if there is persistent focus of infection.

Miscellaneous CNS Infections:**I. Neurosyphilis:**

- It is the tertiary stage of syphilis, caused by *Treponema pallidum*.
- It presents with following major forms:
 - **Meningovascular (within 5 years):**
 - It is characterized by pathologic feature of “endarteritis obliterans”.
 - Presentation:
 - Stroke syndrome – in a relatively young adult
 - Meningitis involving the base of brain:
 - Cranial nerve palsies
 - Hydrocephalus
 - Leptomenigeal granulomas – “gummas”
 - **General Paralysis of Insane (within 5 – 15 years):**
 - It is chronic, progressive fronto-temporal meningoencephalitis with resultant loss of cortical function.
 - Characterized by (PARESIS):
 - Personality changes
 - Affect – apathy, withdrawal, then euphoria, mania
 - Reflexes – bilateral UMN signs (hyper-reflexia).
 - Eye – Argyll-Robertson pupil
 - Sensorium – hallucinations, delusions, illusions
 - Intellect – impaired recent memory, judgement, insight
 - Speech
 - **Tabes Dorsalis (within 5 – 20 years):**
 - Caused by damage to posterior columns & dorsal nerve roots of the spinal cord..
 - Characterized by:

- Loss of pain sensation
- Loss of deep tendon reflexes
- Impaired joint position sense (proprioception) & vibration
- Progressive ataxia – gait is wide-based & slapping
- Argyll-Robertson pupils



Clinical Pearl:

Argyll-Robertson Pupils:

- It refers to bilateral small pupils that **constrict when focusing on near object** (i.e. they accommodate) but do not constrict when **exposed to bright light**.
- Pupils that accommodate, but don't react are said to show "Light-near Dissociation".

▪ Diagnosis:

- CSF Examination:
 - Elevated WBC count > 20 cells/μl – OR:
 - Positive CSF VDRL – OR:
 - Positive CSF intra-theal T. pallidum antibody index

▪ Treatment:

- Injection of procaine benzyl penicillin and probenecid for 17 days.
- Further courses of penicillin are given if condition is not improved.

II. Viral Infections:

<u>Agent</u>	<u>Features</u>
<u>Poliovirus:</u>	<ul style="list-style-type: none"> ▪ Poliovirus: <ul style="list-style-type: none"> ○ Subgroup of enterovirus ○ Transmission = through nasopharynx ○ Incubation period = 7 – 14 days ▪ Causes encephalitis and myelitis. ▪ Destroys anterior horn cell motor neurons (lumber segments). ▪ Descending flaccid paralysis ▪ Death occurs from respiratory failure. ▪ Prevention = live (Sabin) vaccine ▪ Post-polio Syndrome: <ul style="list-style-type: none"> ○ Occurs 25-35 years after initial illness. ○ Characterized by progressive weakness, decreased muscle mass and pain.

Agent	Features
<u>Rabies:</u>	<ul style="list-style-type: none"> ▪ Transmission = dog bite, raccoon bite. ▪ Viral receptor = acetylcholine receptor. ▪ Ascends from bite site by axonal transport to CNS. After CNS replication, it migrates to the saliva. ▪ Disease = encephalitis, presenting with hydrophobia, seizures, coma, death. ▪ Histopathology = Negri bodies ▪ Pre-exposure prophylaxis: <ul style="list-style-type: none"> ▪ Two intra-dermal injections of 0.1 mL human diploid cell vaccine – OR. ▪ Two IM injections given 4 weeks apart, followed by yearly boosters. ▪ Post-exposure prophylaxis: <ol style="list-style-type: none"> 1. Hyperimmune serum (human rabies immunoglobulin): <ul style="list-style-type: none"> ○ The dose is 20 U/kg body weight ○ Half is infiltrated around the bite site. ○ Half is given IM at a different site from the vaccine. OR: 2. Vaccine (human diploid cell vaccine): <ul style="list-style-type: none"> ○ The dose is 1.0 ml given IM. ○ Days – 0, 3, 7, 14, 30 and 90.
<u>Measles:</u>	<ul style="list-style-type: none"> ▪ Subacute sclerosing pan-encephalitis (SSP). ▪ Presents with cognitive decline, spasticity of limbs, and seizures. ▪ CSF = lymphocytic pleocytosis ▪ EEG is distinctively with periodic bursts of tri-phasic waves ▪ Treatment = none (anti-viral therapy is ineffective)

III. Progressive Multifocal Leukoencephalopathy (PML):

- It is viral encephalitis caused by JC polyomavirus.
- The virus infects oligodendrocytes therefore demyelination is the principal pathologic effect.
- Risk Factors:
 - Immunosuppression
 - AIDS when CD4 count is < 50 cell/mm³)
- Clinical Features:
 - Dementia, hemiparesis and aphasia
 - Death within weeks or months.
- Management:
 - Diagnosis:
 - CT scan – areas of low density
 - MRI (T2-weighted Image) – diffuse high signal in the cerebral white matter
 - Treatment:
 - Restoration of immune system.
 - This is done by treating the underlying cause.

Disorders of the Spine & Spinal Cord

Cervical Spondylosis:

- It is the term given to the occurrence of osteoarthritis in the cervical spine.
- It is characterized by degeneration of intervertebral discs and osteophyte formation.

I. Cervical Spondylotic Radiculopathy:

- It occurs when intervertebral disc protrudes **LATERALLY** resulting in compression of a nerve root.
- **Clinical Features:**
 - Pain in the neck
 - Pain radiates in the distribution of the affected nerve root.
 - Neck is held rigidly; neck movements aggravate pain
 - Sensory loss may be found in the affected segment.
 - **Lower motor neuron signs**, including weakness, wasting, and reflex impairment.
- **Management:**
 - Investigations:
 - Best initial test = plain X-ray
 - MRI = most accurate investigation; required if surgery is contemplated.
 - Treatment:
 - Conservation management with analgesics and physiotherapy.
 - Surgery if conservative management fails.

II. Cervical Spondylotic Myelopathy:

- It occurs when intervertebral disc protrudes **DORSOMEDIALY**, resulting in pressure on the spinal cord or the anterior spinal artery, which supplies the anterior two-thirds of the cord.
- **Clinical Features:**
 - Onset = insidious and painless
 - **Upper motor neuron signs**, in which spasticity of legs appear before arms.
 - Sensory loss in upper arms limbs, producing tingling, numbness and proprioception loss in the hands, with progressive clumsiness.
- **Management:**
 - Investigations:
 - Best initial test = plain X-ray
 - MRI or Myelography = if surgery is being considered

- Treatment:

- Surgery – including laminectomy and anterior discectomy.
- Surgery may arrest progression of disability, but may not result in neurologic improvement.

Physical Signs in Cervical Root Compression

<u>Root</u>	<u>Muscle Weakness</u>	<u>Sensory Loss</u>	<u>Reflex Loss</u>
C5	Biceps, Deltoid	Upper lateral arm	Biceps
C6	Brachioradialis	Lower lateral arm, thumb, index finger	Supinator
C7	Triceps, finger & wrist extensors	Middle finger	Triceps

Low Back Pain:

I. Lumbar Disc Herniation:

- Herniation at the L4/5 and L5/S1 level are the most common types.
- **Clinical Features:**
 - Low back pain
 - Pain may radiate to buttock, thigh, calf and foot.
 - Pain is exacerbated by coughing or straining.
 - Pain is relieved by lying flat.
 - Signs:
 - **Femoral nerve stretch test** = pain in the back by hyper-extension of hip.
 - **Lasegue's sign:**
 - Limitation of flexion of the hip on the affected side if straight leg is raised
 - It may be negative if L3 or L4 roots are involved.
- **Management:**
 - **MRI is the investigation of choice.**
 - Treatment:
 - **Conservative Management:**
 - It responds in 90% of patients.
 - Analgesia and early mobilization.
 - Bed rest does not help recovery
 - **Surgery:**
 - If no response to conservative management.
 - If there is sudden onset of symptoms with disturbance of sphincter function.

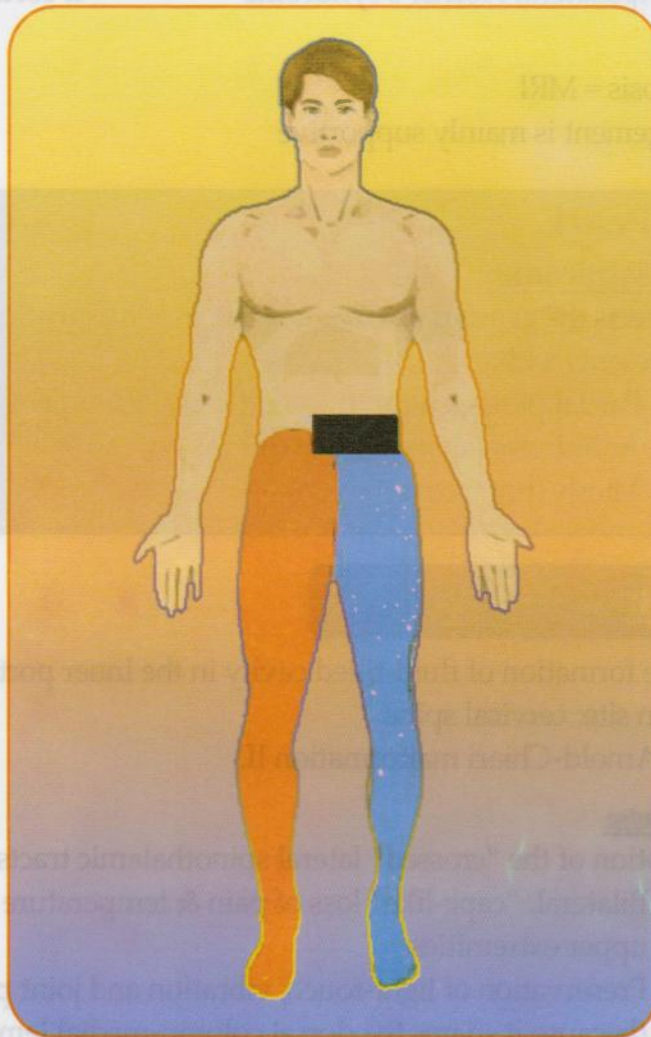
Disc Level	Root	Sensory Loss	Weakness	Reflex Loss
L3/L4	L4	Inner calf	Inversion of foot	Knee
L4/L5	L5	Outer calf & dorsum of foot	Dorsiflexion of toes	None
L5/S1	S1	Sole & lateral foot	Plantar flexion	Ankle

II. Spinal Cord Compression:

- It is a neurological emergency.
- **Causes:**
 - Trauma
 - Malignancy (metastatic disease)
 - Intervertebral disc prolapse.
 - Tuberculosis
- **Clinical Features:**
 - Lower back pain (may be chronic, acute or sub-acute)
 - Localized tenderness over the spine.
 - Hyper-reflexia is found below the level of lesion.
 - Weakness, heaviness, and stiffness of the limbs, mostly the legs.
 - Sensory level, e.g.:
 - Compression at the level of T4 vertebra = loss of sensation below nipples
 - Compression at the level of T10 vertebra = loss of sensation below umbilicus
- **Management:**
 - Investigations:
 - Best initial test in acute spinal cord compression = plain X-ray
 - Most accurate test = MRI spine
 - Treatment depends on cause:
 - Tumors:
 - Best initial step = IV steroids (dexamethasone)
 - Chemotherapy for lymphoma
 - Radiotherapy for solid tumors
 - Surgical decompression if steroids and radiation are not effective
 - Others:
 - TB = surgical excision followed by anti-tuberculous therapy
 - Trauma = specialized neurosurgical treatment.

Brown Sequard Syndrome:

- It refers to lesion in one half of the cord, due to hemisection or unilateral cord lesion.
- **Causes:**
 - Bullet injuries; Stabs
 - Tumor
 - Disc herniation
 - Cervical Spondylosis
 - Multiple sclerosis
 - Neuro-Schistosomiasis



Brown Sequard Syndrome

- Black** = level of lesions (left-sided hemisection) with loss of all sensations
- Blue** = ipsilateral loss of position, vibration, & two-point discrimination
- Red** = contralateral loss of pain & temperature

▪ **Clinical Features:**

- At the Level of lesion:
 - Ipsilateral loss of position & vibration sense.
 - Ipsilateral LMN signs.
- Below the Level of Lesion:
 - Ipsilateral UMN signs - due to corticospinal tract damage
 - Ipsilateral loss of position & vibration - due to dorsal column damage
 - Contralateral pain & temperature loss - due to spinothalamic tract damage
 - Ipsilateral Horner's syndrome - if cord lesion is above T1

▪ **Management:**

- Diagnosis = MRI
- Management is mainly supportive



Clinical Pearl:

Horner's Syndrome:

- It affects the eye and face **from** lesion to sympathetic supply.
- It presents with:
 - Partial ptosis (slight drooping of eyelid: **superior tarsal** muscle)
 - Anhidrosis (absence of sweating)
 - Miosis (pupil constriction)

Syringomyelia:

- It refers to the formation of fluid-filled cavity in the inner portion of the cord.
- Most common site: cervical spine
- Association: Arnold-Chiari malformation II.
- **Clinical findings:**
 - Disruption of the "crossed" lateral spinothalamic tracts:
 - Bilateral, "cape-like" loss of pain & temperature sensations in upper extremities
 - Preservation of light-touch, vibration and joint position sensation (because it spares the dorsal column-medial lemniscus).
 - Disruption of anterior horn cells that results in:
 - Weakness and atrophy of intrinsic muscles of hand (Claw-Hand).
 - Followed by wasting and weakness of arms, shoulders, and respiratory muscles.

- Must be differentiated from Amyotrophic lateral sclerosis (ALS), in which there are no sensory changes.
- Other Signs:
 - Horner's syndrome
 - Upper motor neuron (UMN) leg signs.
 - Syringobulbia – brainstem involvement.
 - Charcot's (neuropathic) joints
- **Management:**
 - Investigation of choice = MRI
 - Treatment of choice = Surgery

Peripheral Lesion (Intracranial Facial Palsy)	Central Lesion (Extracranial Facial Palsy)
Unilateral weakness of the entire face	Unilateral weakness of the lower half of face
Loss of taste	Loss of taste
Cannot smile – mouth droops to the paralysed side	Cannot smile – mouth droops to the paralysed side
Cannot fully open the mouth	Cannot fully open the mouth
Flat nasolabial fold	Flat nasolabial fold
Cannot wrinkle the forehead or raise eyebrows	Can wrinkle the forehead and raise eyebrows
Eyes closed, but eyelids roll up	Eyes close
Bell's phenomenon present	Bell's phenomenon absent
Taste affected (if cranial trigeminal is involved)	Taste not affected
Parietal hyperaesthesia – (pain & tingling)	Hearing not affected
Normal facial reflexes	Increased facial reflexes (elicited by tapping around the mouth)
Atrophy of facial muscles	No atrophy of facial muscles

Diseases of Peripheral Nerves

I. Bell's Palsy:

- It refers to acute, idiopathic, unilateral facial nerve palsy (peripheral cranial nerve VII).
- It is postulated to be due to reactivation of Herpes simplex virus (HSV)-1.
- **Clinical Features:**
 - All the features of intra-nuclear facial palsy (see table below)
 - Taste dysfunction – reduced
 - Hearing dysfunction – hyperacusis (involvement of nerve to stapedius).
 - Tearing – increased due to:
 - Weakness of orbicularis oculi
 - Lacrimal gland dysfunction
 - Vesicles in the ear or on the palate indicate that facial palsy is due to herpes zoster rather than Bell's palsy.
- **Treatment:**
 - Prednisolone 40 – 60 mg daily for a week speeds recovery if given within 72 hours.
 - About 80% of patients recover spontaneously within 12 weeks.

Central Lesion (Supranuclear Facial Palsy)	Peripheral Lesion (Infranuclear Facial Palsy)
Contralateral weakness on the lower half of face	Ipsilateral weakness of the entire hemi-face.
Cannot smile – mouth droops to the paralyzed side	Cannot smile – mouth droops to the paralyzed side
Cannot fully open the mouth Flat nasolabial fold	Cannot fully open the mouth Flat nasolabial fold
Can wrinkle the forehead and raise eyebrows	Cannot wrinkle the forehead or raise eyebrows
Eye does close	Eye doesn't close, eyeball rolls up
Bell's phenomenon absent	Bell's phenomenon present
Taste not affected	Taste affected (if chorda tympani is involved)
Hearing not affected	Ipsilateral hyperacusis – (nerve to stapedius)
Increased facial reflexes (elicited by tapping around the mouth)	Normal facial reflexes
No atrophy of facial muscles	Atrophy of facial muscles

II. Carpal Tunnel Syndrome:

- It is the most common entrapment neuropathy.
- It results from compression of median nerve at the level of the wrist within carpal tunnel.
- It is more common in women and is frequently bilateral.
- **Risk factors:**
 - Pregnancy; Hypothyroidism
 - Amyloidosis; Diabetes mellitus
 - Acromegaly; Arthritis
 - Repetitive motions of the wrist.
- **Clinical Features:**
 - Pain (mostly nocturnal), numbness, or paraesthesias in the thumb, index, middle, and radial side of ring finger.
 - Ape hand appearance – due to thenar muscle atrophy
 - Difficulty opposing the thumb with the little finger.
 - **Tinel's sign** = pain reproduced by tapping over median nerve.
 - **Phalen sign** = pain reproduced with forced flexion of the wrist.

R_x

Treatment:

- Best initial therapy = wrist splints to immobilize the hand, NSAIDs.
- Avoid manual activity
- Steroid injections if NSAIDs and splints do not control symptoms.
- Surgical decompression

III. Guillain-Barre' Syndrome (GBS):

- Also known as “**acute inflammatory demyelinating polyradiculoneuropathy**”.
- It is an acute, rapidly progressive, acquired demyelinating autoimmune disease of peripheral nerves.
- It is the most common acute peripheral neuropathy
- **Pathogenesis:**
 - It is an autoimmune demyelination syndrome.
 - It is due to T-cell mediated immune response, accompanied by segmental demyelination induced by activated macrophages.
 - It is associated with infections caused by:
 - *Campylobacter jejuni* – most common.
 - Cytomegalovirus
 - Epstein-Barr virus
 - *Mycoplasma pneumoniae*

▪ **Clinical findings:**

- Symmetric ascending paralysis (distal to proximal).
- Loss of deep tendon reflexes.
- Facial and bulbar weakness
- Respiratory weakness requiring ventilator support – 20% cases.
- Autonomic dysfunction e.g. orthostatic hypotension, arrhythmia, sweating.
- **Miller – Fischer Variant GBS:**
 - Ophthalmoplegia
 - Ataxia
 - Areflexia

▪ **Diagnosis:**

- CSF findings:
 - **Albuminocytologic Dissociation** i.e.:
 - CSF protein is elevated (>55 mg/dL), but
 - No rise in number of cells.
- Electromyography:
 - It is the most accurate test.
 - It shows decreased conduction velocity.

R_x

Management:

- Regular monitoring of respiratory function.
- Ventilation is needed if vital capacity falls below 1L.
- **Plasmapheresis (i.e. plasma exchange) within the first 14 days – OR.**
- **Intravenous immunoglobulin (IVIG) within the first 14 days.**
- There is NO BENEFIT in combining IVIG with Plasmapheresis.

Clinical Pearl:

GBS Mnemonic: 5 A's

- Acute inflammatory demyelinating polyradiculopathy.
- Ascending paralysis
- Autonomic dysfunction
- Albuminocytologic dissociation
- Areflexia



Clinical Pearl:

Definitions:

- "Mononeuropathy" – involvement of one nerve.
- "Mononeuropathy Multiplex" – involvement of ≥ 2 , separate, non-contiguous nerves.
- "Polyneuropathy" – involvement of multiple symmetric nerves.

Diseases of Neuromuscular Junction:

I. Myasthenia Gravis:

- It is an autoimmune disease caused by antibodies against **post-synaptic** acetylcholine receptors.
- It is type-II hypersensitivity reaction.
- **Clinical Features:**
 - Asymmetric muscle weakness.
 - **Weakness is aggravated with activity as the day progresses.**
 - Weakness is relieved with rest.
 - Ptosis & diplopia due to fatigue of extraocular muscles is often the first symptom.
 - Signs:
 - Deep tendon reflexes = normal
 - Papillary response = normal
 - Sensory abnormality = none
 - Autonomic dysfunction = none
 - Affected age group:
 - Young (20 – 30 years) = more common in women.
 - Old (60 – 70 years) = more common in men.
- **Association:**
 - Thymic hyperplasia in 65%
 - Thymoma in 15%.
- **Diagnosis:**
 - Tensilon Test:
 - It involves intravenous injection of edrophonium, which is anti-cholinesterase.
 - It results in rapid improvement of symptoms (within 30 seconds).
 - It is NOT routinely used.
 - Electromyography:
 - It is the most accurate test.
 - It shows a **decremental response** to repetitive nerve stimulation.
 - Antibodies:
 - Acetylcholine-receptor antibodies (AChRA) – (80 – 90%).
 - Anti-MuSK antibodies – in AChRA-negative patients with predominant bulbar involvement.

R_x**Treatment:**

- Anti-cholinesterase Agents:
 - These agents are best initial therapy.
 - These agents prolong the duration of action of acetylcholine at NMJ.
 - The most commonly used agent is pyridostigmine.
- Immunologic Treatments:
 - Acute (Emergency) Treatment:
 - Plasmapheresis – OR.
 - IV immune globulin (IVIG)
 - Chronic Treatment:
 - Prednisolone
 - Immunosuppressants – azathioprine, cyclophosphamide
 - Thymectomy – indications:
 1. Thymoma
 2. Antibody-positive patients < 45 years, PLUS:
 - Symptoms not confined to extraocular muscles, OR:
 - Extraocular muscle involvement with disease established for >7 years.
- **Myasthenic Crisis:**
 - It refers to exacerbation of myasthenia.
 - It presents with severe weakness, with potentially lethal complications of respiratory failure and aspiration.
 - Tensilon Test – improvement of symptoms with edrophonium.
 - Treatment:
 - Immunosuppression with glucocorticoids
 - IVIG – OR – plasma exchange.
- **Cholinergic Crisis:**
 - It is due to over-dosage of anti-cholinesterase drugs.
 - It presents with muscle fasciculation, paralysis, pallor, sweating, excessive salivation and constricted pupils.
 - Treatment:
 - Withdrawal of anti-cholinesterase drugs
 - Endotracheal intubation if respiratory paralysis (follow FVC)



Clinical Pearl:

Myasthenia Gravis:

- Myasthenia gravis is associated with Thymoma.
- Therefore all newly diagnosed patients **should undergo** chest CT to evaluate for Thymoma.
- Resection of Thymoma can be curative in up to 85% of cases..

II. Lambert-Eaton Myasthenic Syndrome:

- It is an autoimmune disease caused by antibodies against **pre-synaptic** calcium channels in the neuromuscular junction.
- It is associated with underlying malignancy, most commonly **small cell lung carcinoma (60%)**.
- **Clinical Features:**
 - Proximal muscle weakness
 - Weakness improves with activity, but not with rest (in contrast to myasthenia gravis)
 - Extraocular, bulbar, and respiratory muscles are typically spared.
 - Cardinal Sign:
 - Absence of deep tendon reflexes (DTRs).
 - DTRs return immediately after sustained contraction of the relevant muscle.
- **Diagnosis:**
 - Electromyography = **incremental response (post-tetanic potentiation of motor response)** to repetitive nerve stimulation.
 - Autoantibodies to presynaptic calcium channels.
 - Chest CT (lung cancer)
- **Treatment:**
 - 3, 4 – diaminopyridine or Pyridostigmine
 - Immunosuppressants
 - Treat small cell lung cancer

Chapter 14

DERMATOLOGY



Definitions

<u>Term</u>	<u>Definition</u>
Macule	It is a flat, non-palpable lesion with changes in skin color, < 1 cm.
Patch	It is a flat, non-palpable lesion with changes in skin color, > 1 cm.
Papule	It is a solid, elevated lesion < 0.5 cm
Nodule	It is a solid, elevated lesion > 0.5 cm
Plaque	It is an elevated, palpable, flat-topped lesion ≥ 1 cm
Vesicle	It is a fluid (serous) filled raised lesion ≤ 1 cm.
Bulla	It is a fluid (serous) filled raised lesion > 1 cm.
Pustule	It is pus-filled raised lesion.
Cyst	A nodule consisting of an epithelial-lined cavity filled with fluid or semi-solid material.
Scale	A thin flake of dead exfoliated epidermis.
Crust	The dried residue of skin exudates such as serum, pus, and blood.
Erosion	Non-scarring loss of superficial epidermis.
Excoriation	Scratch mark (erosions caused by scratching)
Fissure	A linear crack in the skin, often resulting from excessive dryness.
Lichenification	Chronic thickening of skin with increased skin markings.
Ulcer	A circumscribed loss of skin extending into the dermis.
Erythema	Redness of skin due to vascular dilatation
Petechia	It is a pinpoint (1-2 mm) macule of blood (extravasation of blood) It does NOT blanch with pressure.
Purpura	It is a macule or papule of blood in the skin. It is larger than petechia and does NOT blanch with pressure.
Ecchymosis	Large confluent area of purpura ("bruise")
Telangiectasia	Abnormal visible dilatation of blood vessels.

Allergic & Immune-mediated Disorders

I. Urticaria (Hives):

- It is characterized by superficial, intense erythema and edema in a localized area.
- It results from the release of vasoactive mediators (histamine) from mast cells in a type-I hypersensitivity reaction (IgE-mediated).

- Classification:

- If the individual lesion lasts < 24 hours = urticaria
- If the individual lesion lasts > 24 hours = urticarial vasculitis.
- If the condition is present for < 6 weeks = acute urticaria
- If the condition is present for > 6 weeks = chronic urticaria

- Triggers (antigens):

- Pollens
- Foods
- Drugs (salicylates, antibiotics, ACE-inhibitors, codeine)
- Insect venoms
- Urticarial vasculitis:
 - Idiopathic
 - SLE
 - **Hepatitis B:**
 - As a part of serum sickness prodrome.
 - This is a type-III hypersensitivity reaction.

- Clinical Features:

- **Dermatographism** i.e. urticaria develops in areas of mechanical pressure on skin (e.g. trunk, distal extremities, and ears).
- **Angioedema:**
 - It refers to deeper, more diffuse swelling.
 - IgE-mediated angioedema is associated with urticaria.
 - Complement-mediated angioedema is also called hereditary angioedema, and is due to C1 inhibitor deficiency.

- Morphology:

- Superficial dermal edema.
- **Edema is localized to perivascular spaces of superficial dermis.** (unlike eczema)

R_x**Treatment:**

- Non-sedating anti-histamines i.e. H1-blockers (e.g. loratidine) = mainstay of treatment
- Cases refractory to H1 blockers = H2 blockers (e.g. cimetidine)
- Stop precipitating drugs.
- Those with features of angioedema should carry a kit for self-administration of adrenaline

II. Eczema:

- It is derived from Greek word, meaning "to boil over".
- It consists of pathogenetically different conditions that consist of red, papulovesicular, oozing, and crusted lesions that with persistence develop into raised and scaling plaques.
- It is synonymous with the word "Dermatitis" and the two words are interchangeable.
- Morphology:
 - **Spongiosis** i.e. intercellular edema of epidermis.
 - Edema isn't localized as in urticaria, but instead seeps into the intercellular of epidermis, splaying the keratinocytes apart.

▪ **Classification:**

<u>Endogenous</u>	<u>Exogenous</u>
Atopic eczema (dermatitis)	Irritant contact eczema
Discoid dermatitis	Allergic contact eczema
Hand dermatitis ("pompholyx")	Photosensitive eczema
Seborrhoeic dermatitis	Lichen simplex
Venous (gravitational) dermatitis	
Asteatotic eczema	

(i). Atopic Dermatitis:

- It is a relapsing inflammatory skin disorder.
- It is a genetically complex, familial disease with a strong maternal influence.
- Pathogenesis:
 - The exact pathophysiology is not fully understood.
 - There is an initial activation of Th2 – CD4 lymphocytes in the skin which drives the inflammatory process.

▪ **Clinical Features:**

- Itchy erythematous scaly patches leading to lichenification.
- In children it starts on the face before spreading to body.
- In adults it involves the flexural surfaces such as in front of the elbows and ankles, behind the knees, and around the neck.
- Family history of hay fever, asthma, or eczema

R_x

Treatment:

- General Measures:
 - Avoidance of irritants and allergens
 - Emollients to keep skin moist
 - Wearing cotton clothes
 - Moisturizing soap substitute
- Topic Therapies:
 - Steroids
 - Immunomodulators e.g. tacrolimus ointment.
- Adjunct Therapies:
 - Oral antibiotics
 - Sedating anti-histamines at night (e.g. hydroxyzine hydrochloride)
 - Paste bandaging

(ii). Seborrheic Dermatitis:

- It is chronic inflammatory dermatoses.
- Pathogenesis:
 - It is caused by overgrowth of fungus, **Malassezia furfur (Pityrosporum ovale)**, together with a strong cutaneous immune response to this yeast.
- **Clinical Features:**
 - It has a predilection for areas with oily skin.
 - Dandruff in adults, "**Cradle cap**" (thick crust on scalp) in infants.
 - **Leiner disease** (generalized seborrheic dermatitis along with diarrhea & failure to thrive)
 - It is more common in Parkinsonism as well as in HIV disease.
 - Common sites:
 - Scalp (most common); Forehead
 - External auditory canal; Retro-auricular area; Nasolabial folds

R_x**Treatment:**

- Combination of steroid ointment + topical antifungal cream
- 2% sulphur + 2% salicylic acid can be added to help control resistant cases.
- Ketoconazole shampoo for the scalp.
- Emollients and a soap substitute are useful adjuncts.

(iii). Contact Dermatitis:

- It is a type-IV hypersensitivity reaction that results from contact with an allergen to which the patient has previously been exposed and sensitized.
- **Types:**
 - Allergic contact dermatitis:
 - It occurs after repeated exposure to a chemical substance.
 - It occurs ONLY in those who are susceptible to develop allergic reaction.
 - Common causes are:
 - Nickel (in costume jewelry)
 - Chromate (in cement)
 - Latex (in surgical gloves)
 - Perfumes
 - Irritant contact dermatitis:
 - It occurs after repeated exposure to irritant.
 - It can occur in ANY individual.
 - Common causes are:
 - Detergents
 - Soaps
 - Bleach
 - Alkalis, acids
- **Treatment:**
 - Same as for atopic dermatitis (see above)
 - Strict avoidance of any causative agent.

(iv). Other Types of Dermatitis:

- **Venous (Gravitational) Eczema:**
 - It occurs on the lower legs.
 - It is due to chronic venous hypertension.
 - It is associated with signs of venous insufficiency such as:
 - Edema
 - Loss of hair
 - Red or bluish discoloration
 - Hemosiderin pigmentation and ulceration

▪ **Asteatotic Eczema:**

- Also known as "Senile Eczema".
- It occurs on the lower legs in the elderly people.
- It is characterized by dry plate-like ("crazy paving" pattern) cracking of the skin with a red eczematous component.

III. Psoriasis:

- It is a T-cell mediated disease that involves increased keratinocyte proliferation alongwith inflammation and angiogenesis.

▪ **Clinical findings:**

- Erythematous (salmon-colored) plaques covered with silvery white scales
- Occurs on extensor surfaces such as **elbows and knees** (most common sites)
- Nail changes (e.g. **fungernail pitting**) in 30% of cases.
- Strong association with streptococcal pharyngitis.
- **Koebnerization** i.e. new plaques occur at sites of repeated trauma.
- **Auspitz sign** i.e. visible pinpoint bleeding when scale is removed from plaque due to thin epidermis above dermal papilla.
- Associations:
 - Arthritis
 - Spondylitic joint disease (seronegative arthritis)
 - Myopathy
 - Enteropathy
 - AIDS

▪ **Classification:**

- Stable plaque psoriasis – it is the most common type.
- Flexural psoriasis – it occurs on flexor surfaces such as groin, natal cleft, and sub-mammary area.
- Guttate psoriasis:
 - It is "Raindrop-like" psoriasis.
 - It is most commonly seen in children and young adults.
 - It is characterized by eruption of plaques over the trunk about 2 weeks after a streptococcal sore throat.
- Erythrodermic & Pustular Psoriasis:
 - These are the most severe types of psoriasis and are dermatologic emergency.
 - They can occur together, and called "**Von Zumbusch**" psoriasis.
 - Erythrodermic form:
 - Over 90% of body surface becomes erythematous and scaly.

R_x

- It is associated with malaise, fever, and circulatory disturbance.
- Pustular Form:
 - It presents with many sterile pustules on an erythematous base.
 - It is more common in females, and heavy cigarette smokers.

Treatment:

- Topical Agents:
 - Dithranol, tar, vitamin D analogues (calcitriol)
 - Corticosteroids
- Phototherapy:
 - Ultraviolet B
 - Psoralen (photosensitizer) plus ultraviolet A (PUVA)
- Systemic Agents:
 - Acitretin (a retinoid)
 - Methotrexate and cyclosporin
- Biologic Agents:
 - Infliximab
 - Etanercept
- Regimens:
 - The "Goeckerman Regimen" = tar + UVB.
 - The "Ingram Regimen" = dithranol + UVB.

Clinical Pearl:

Site of Rash:

- A rash commonly involving the EXTENSOR surfaces = think of psoriasis.
- A rash commonly involving the FLEXOR surfaces = think of atopic dermatitis

Cutaneous Manifestations of Systemic Diseases

I. Erythema Nodosum:

- It is the **most common cause of panniculitis** (inflammation of dermis and subcutaneous layer)
- It characteristically presents with **painful, erythematous nodules on lower legs** and sometimes forearms.
- **Associations:**
 - Infections (Mycoplasma, Chlamydia)
 - Drugs (sulfonamides, oral contraceptive pills)
 - Inflammatory bowel disease
 - Sarcoidosis
 - Behcet's disease
 - Tuberculosis
 - Leprosy

R_x

Treatment:

- NSAIDs
- Light compression bandaging and bed rest.
- Treat underlying disease.
- Resistant cases require dapsone, colchicine, or prednisolone.

II. Erythema Multiforme:

- It is immunologic (hypersensitivity) reaction of skin.
- It is characterized by diffuse, erythematous **target-like lesions in many shapes**.
- **Associations:**
 - Herpes simplex infection – most common identifiable cause
 - Mycoplasma infection
 - Drugs (sulfonamides, penicillin, barbiturates, antimalarials)
 - Carcinomas and lymphomas
 - HIV infection
 - Wegener's granulomatosis
 - Collagen vascular disease (SLE, dermatomyositis)
- Severe Forms:
 - **Stevens-Johnson Syndrome (SJS):**
 - It is a life-threatening exfoliative mucocutaneous disease.

- It is associated with epidermal separation of < 10% of body surface area.
 - It is always associated with mucosal lesions.
 - It is associated with fever and skin tenderness.
 - Biopsy shows degeneration of basal layer of epidermis.
- **Toxic Epidermal Necrolysis (TEN):**
- It is a life-threatening exfoliative mucocutaneous disease.
 - It is associated with epidermal separation of > 30% of body surface area.
 - It is always associated with mucosal lesions.
 - It is associated with fever, skin tenderness, hypotension, and decreased consciousness.
 - Biopsy shows full-thickness eosinophilic epidermal necrosis.

R_X**Treatment:**

- Treat the underlying cause.
- Recurrent erythema multiforme can be treated with prophylactic oral acyclovir.
- SJS and TEN:
 - Short course of intravenous immunoglobulin (IVIG).
 - Corticosteroids have shown NO benefit.

III. Pyoderma Gangrenosum:

- It is a condition of unknown etiology.
- It presents with erythematous nodules or pustules which frequently ulcerate.
- It is characterized by ulcers, which are:
 - "Gangrenous" i.e. typical bluish black undermined edge
 - "Pyoderma" i.e. purulent surface.
- **Associations:**
 - Inflammatory bowel disease – most common
 - Rheumatoid arthritis
 - Multiple myeloma, lymphoma, leukemia
 - Primary biliary cirrhosis

Rx

Treatment:

- Treat the underlying condition.
- Treatment options are:
 - Potent topical steroids;
 - 0.1% Tacrolimus
 - Oral dapsone and minocycline
 - Cyclosporine

IV. Acanthosis Nigricans:

- It refers to thickened, velvety, hyperpigmented zones of skin.
- It most commonly involves the flexural areas (axilla, groin, anogenital regions).
- Types:
 - Benign Type:
 - It affects young people (childhood, puberty)
 - It is associated with obesity, diabetes, pituitary tumors, and pineal tumors.
 - Malignant Type:
 - It affects old people.
 - It is associated with gastrointestinal malignancy, most commonly stomach adenocarcinoma.

Bullous Diseases

I. Dermatitis Herpetiformis:

- It an autoimmune blistering disorder, affecting males more than the females
- It has strong association with **celiac disease**.
- Pathogenesis:
 - Antigen: Gliadin
 - Antibody: IgA
- Diagnosis:
 - It presents with intensely itchy blisters of the skin.
 - It has predilection for the elbows, extensor forearms, scalp, and buttocks.
 - Direct immunofluorescence = **granular deposits of IgA** in the tips of dermal papillae.
 - Skin biopsy:
 - Blister: subepidermal blister
 - Neutrophil microabscesses in the dermal papilla.

▪ **Treatment:**

- Gluten-free diet (if patient has celiac disease)
- Oral dapsone or sulphonamides

II. Pemphigus & Bullous Pemphigoid:

<u>Pemphigus</u>	<u>Bullous Pemphigoid</u>
It is an autoimmune blistering disorder.	It is an autoimmune blistering disorder.
Anatomic site = intra-epidermal	Anatomic site = basement membrane zone.
Mucosal involvement = common	Mucosal involvement = rare
Age = young (20 – 60 years)	Age = old (>60 years)
Mortality = high (acts like burn)	Mortality = low
Antigen = Desmoglein 3 (desmosomes)	Antigen = Hemidesmosomes
Antibody: IgG	Antibody: IgG
Clinical Features: <ul style="list-style-type: none"> ▪ Flaccid blisters. ▪ Blisters are NOT itchy ▪ Blisters rapidly denude. ▪ Thus it presents with erythematous weeping erosions. 	Clinical Features: <ul style="list-style-type: none"> ▪ Large tense bullae ▪ Blisters are very itchy ▪ Mucosal ulceration is uncommon. ▪ Blisters are tense and therefore don't rupture easily.
Direct immunofluorescence = fishnet-like (tombstone) pattern of immunoglobulins surrounding epidermal cells.	Direct immunofluorescence = linear deposition of immunoglobulins along the basement membrane with increased eosinophils in dermis.
Treatment: <ul style="list-style-type: none"> ▪ Rituximab + intravenous immunoglobulin ▪ High dose oral prednisolone ▪ Steroid sparing agents such as azathioprine. 	Treatment: <ul style="list-style-type: none"> ▪ High dose oral prednisolone ▪ Steroid sparing agents such as azathioprine.



Clinical Pearl:

Nikolsky's Sign:

- It refers to separation of the superficial skin layers with slight rubbing.
- It is seen in:
 1. Pemphigus
 2. Stevens-Johnson syndrome
 3. Toxic epidermal Necrolysis

Skin Tumors

I. Malignant Melanoma (MM):

- It is the malignant tumor of the melanocytes.
- It is usually asymptomatic, but itching may be the first symptom.
- It is more common in men, where they occur on the upper back.
- In women they occur on both the back and the legs.
- It is due to mutations in chromosome 9 that encodes p16INK4A.

Risk Factors:

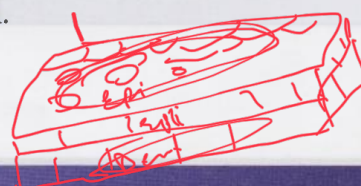
- Sunlight – most important risk factor
- Hereditary factors (history in first-degree relatives)
- Dysplastic nevus syndrome
- Carcinogens
- Xeroderma pigmentosum
- Male gender

Clinical Features:

- Signs (ABCDE):
 - Asymmetry
 - Borders irregular
 - Color changes
 - Diameter more than 10 mm
 - Elevated
- Clinical Warning Signs:
 - Enlargement of a pre-existing mole
 - Itching or pain in the pre-existing mole.
 - Development of a new pigmented lesion during adult life.
 - Irregular borders.
 - Variegation of colors within pigmented lesion.

Morphology:

- Phases of Growth:
 - (i). Radial Growth Phase:
 - It is the initial phase of invasion.
 - It involves horizontal growth within epidermis and superficial dermis.
 - It has no metastatic potential.



(ii). Vertical Growth Phase:

- It is the final phase of invasion.
- It involves growth of melanoma downward into the deeper layers.
- It has metastatic potential, and determines the biologic behavior of melanoma.

○ Sub-types:

- **Superficial spreading melanoma – most common type.**
- Acral lentiginous melanoma – most common on hands and feet.
- Nodular melanoma – no radial growth, therefore, poor prognosis.
- Lentigo maligna melanoma – most common sun-damaged skin of the face of elderly.

Rx

Treatment:

- Surgery is the only curative treatment.
- Melanoma < 1 mm = surgical excision + 1 cm margin
- Melanoma > 1 mm = surgical excision + 3 cm margin

II. Squamous Cell Carcinoma (SCC):

- It is the second most common skin malignancy after **basal cell carcinoma**.
- It has a higher incidence in men than in women.
- Human papillomavirus (HPV type-36) have been detected in potential precursors of SCC.
- Minimal risk for metastasis (less than 5%)

▪ **Risk factors:**

- UV light (DNA damage)
- Actinic keratosis
- Arsenic exposure
- Old burn scars
- Ulcers and draining osteomyelitis.

▪ **Morphology:**

- Usually well-differentiated
- Usually nodular and ulcerated
- Tumor cells are enlarged with angulated contours
- Unlike actinic keratosis, the cells with atypical nuclei lie "at all" levels of epidermis.
- Dyskeratosis (single-cell keratinization) – "keratin pearls".

#1 Basal Cell CA
#2 Squamous Cell CA.

Rx

Treatment:

- Surgical excision
- Radiotherapy
- Curettage should be avoided.

III. Basal Cell Carcinoma (BCC):

- It is **the most common skin malignancy**.
- It is a slow-growing tumor that rarely metastasizes, but is locally aggressive and infiltrative, therefore also called "**Rodent ulcer**".
- It presents as pearly-papules containing prominent, dilated subepidermal blood vessels (telangiectasia).
- **Risk factors:**
 - Chronic sun exposure
 - Lightly pigmented individuals
 - Xeroderma pigmentosum
 - Immunosuppression
- **Morphology:**
 - Two patterns of growth; multifocal lesions and nodular lesions.
 - Arises from the basal cell layer of the epidermis.
 - Basophilic basal cells infiltrate the underlying dermis.
 - Basal cells tumors have "**palisading nuclei**".

Rx

Treatment:

- Surgical excision with a 3 – 5 mm border.
- Recurrent tumor = Mohs' micrographic surgery

Skin Infections

Viral Disorders:

- Warts = human papillomavirus (HPV)
- Molluscum contagiosum = Poxvirus (DNA virus)
- Measles = Measles virus (RNA paramyxovirus)
- Rubella = RNA togavirus
- Erythema infectiosum (fifth disease) = Parvovirus B19

Bacterial Disorders:

I. Furuncle & Carbuncle:

- Furuncle = pus collection in 1 hair follicle, most commonly caused by *S. aureus*
- Carbuncle = pus collecting in many hair follicles

II. Cellulitis & Necrotizing Fasciitis:

- Cellulitis:
 - It refers to acute, painful spreading infection of dermis and subcutaneous tissues.
 - It is most commonly caused by *S. aureus*, and streptococcus pyogenes.
- Necrotizing Fasciitis:
 - It is deep infection along fascial planes with severe pain, fever, and leukocytosis.
 - It is usually a polymicrobial infection that includes *S. aureus*, *E. coli*, and *Clostridium perfringens*.
 - It is associated with **crepitus** due to methane and CO₂ production.

III. Toxic Shock Syndrome (TSS) & Scarlet Fever:

- Toxic-Shock Syndrome:
 - It is caused by production of toxic shock syndrome toxin (TSST) by *S. aureus*.
 - It usually occurs in tampon-using menstruating women.
 - Clinical Features:
 - Desquamating, sunburn-like rash
 - Fever and hypotension.
- Scarlet fever:
 - It is caused by *Strep. Pyogenes*
 - **"Sunburn with goose bumps rash"** i.e. finely punctate, erythematous, but blanches with pressure.
 - Strawberry-tongue and circumoral pallor.
 - **Pastia's line** = rash, most intense on creases of axilla and groin

IV. Acne & Impetigo:

- Acne:
 - It refers to inflammation of pilo-sebaceous unit.
 - It is caused by secondary **Propionibacterium acnes** infection of blocked pore.
- Impetigo:
 - It refers to superficial infection of epidermis.
 - It is characterized by pustules and **honey-colored crusts** on an erythematous base.
 - It is microscopically characterized by **neutrophils beneath stratum corneum**.
 - It is characterized by blisters, which are due to breakdown of **desmoglein-1 by toxin**.
 - Agents:
 - Most common overall = *S. aureus*
 - Bullous type = *S. aureus*
 - Non-bullous type = *Streptococcus pyogenes*
 - Treatment:
 - Topical Mupirocin, OR
 - Topical Fusidic acid

Fungal Disorders:

I. Dermatophytoses:

- It is superficial fungal infection.
- It is confined to stratum corneum or its adnexal structures.
 - Tinea capitis = dermatophyte infection of scalp (*Trichophyton tonsurans*)
 - Tinea barbae = dermatophyte infection of beard.
 - Tinea pedis (athlete's foot) = infection of foot (*Trichophyton rubrum*)
 - Tinea cruris (jock itch) = infection of groin (*Trichophyton rubrum*)
 - Tinea corporis = infection of body (also known as "ringworm")
 - Onychomycosis = infection of nails (*Candida albicans*)

II. Tinea Versicolor:

- It is dermatophyte infection caused by *Malassezia furfur* (aka *Pityrosporum ovale*).
- It is associated with humidity and sweaty conditions (e.g. cooking)
- It is presents with sharply demarcated **hypopigmented and hyperpigmented macules**.
- Hypopigmentation is due to decreased melanin synthesis, while hyperpigmentation is due to enlargement of melanosomes
- Potassium hydroxide (KOH) preparation shows yeast and hyphae with classic **spaghetti and meatball appearance**.

Infestations:

- Onchocerciasis (leopard skin) = *Onchocerca volvulus*
- Filariasis = *Wuchereria bancrofti*
- Schistosomiasis (swimmer's itch) = *Schistosoma*
- **Cutaneous larva migrans:**
 - It is also known as "Creeping Eruption".
 - It presents as pruritic, serpiginous thread-like lesion marking burrow of migrating nematode larvae, often on back, hands, feet, and buttocks.
 - Organism = *Strongyloides*, hookworms, *Ancylostoma*, *Necator*.
- **Scabies:**
 - It is caused by ***Sarcoptes scabiei***.
 - Clinical Features:
 - It presents with markedly, pruritic papules and "**burrows**" located intertriginous areas (e.g. finger and toe webs, groin).
 - Pruritis is worse at night.
 - Lesions are contagious.
 - Excoriations and secondary bacterial infection may complicate the rash.
 - **Norwegian Scabies:**
 - It is "crusted" scabies.
 - It is seen in immunocompromised patients where huge number of mites are carried in the skin
 - Treatment:
 - Application of topical scabicide:
 - 5% permethrin
 - It is washed off after 10 hours.
 - Malathion
 - Benzylbenzoate
 - Lindane

Chapter 15

PSYCHIATRY



Schizophrenia

I. Definitions:

▪ Delusions:

- It is defined as a fixed (i.e. resistant to change, even in the face of overwhelming contradictory evidence), false belief.
- Delusion is broadly categorized into two types:

(i) Non-Bizarre Delusions:

- These delusions while not true have the possibility of being true and their content is understandable.

(ii). Bizarre Delusions:

- These delusions are clearly implausible, i.e., they have no possibility of being true and their content is not understandable.
- Delusion can be further characterized based on the "content":

<u>Delusion Content</u>	<u>Description</u>
<u>Delusions of Reference:</u>	These are beliefs that random or neutral events are not random or neutral, but include the individual in a special way. Example: patient thinks that on the news channel certain words are meant to deliver a special message to him
<u>Delusions of Grandiosity:</u>	These are beliefs that one has some special significance or power.
<u>Paranoid Delusions:</u>	These are beliefs that one is being harmed or persecuted by a particular person or a group of people.
<u>Nihilistic Delusions</u>	These are bizarre beliefs that one is dead or one's body is breaking down or that one does not exist.
<u>Erotomaniac delusions</u>	These are erroneous beliefs that the patient has a special relationship with someone.

▪ **Hallucinations:**

- It is defined as the perception of a sensory process in the absence of an external source.
- Types:
 - Auditory (typical hallucination in Schizophrenia)
 - Visual
 - Somatic (include feelings of being touched, or sexual intercourse, or of pain).
 - Olfactory
 - Gustatory

▪ **Disorganization:**

- Disorganization in behavior and thinking can be seen in schizophrenia
- The symptoms of disorganization can be:
 - **"Tangential Speech"** – the patient gets increasingly further off the topic without appropriately answering a question.
 - **"Circumstantial Speech"** – the patient person will eventually answer a question, but in a markedly roundabout manner.
 - **"Derailment"** – the patient suddenly switches topic without any logic or segue.
 - **"Neologisms"** – it refers to creation of new, idiosyncratic words.
 - **"Word salad"** – Words are thrown together without any sensible meaning.

II. Schizophrenia:

(i). Introduction:

- It is a thought disorder characterized by delusions, hallucinations, and lack of insight.
- It is a neurodevelopmental disorder, caused by brain developmental abnormalities, genetic predisposition, environmental influences & triggers.
- It is a syndrome with several symptom domains, including:
 - Positive symptoms
 - Negative symptoms
 - Cognitive impairment
 - Mood & anxiety symptoms
- **Demographics:**
 - It occurs in all ethnic groups with a prevalence of 0.5%
 - It is more common in men (1.5:1).
 - It typically presents in 20-30s, but can present late – especially in women.

- Risk of disease in children of an affected parent = 10%
- Risk of disease in identical twin = 50%

▪ **Pathogenesis & Risk Factors:**

- Strong genetic predisposition.
- Obstetric complication at the time of birth.
- Urban upbringing
- Decreased brain size –with greater reduction of temporal lobe volume.

(ii). Diagnosis:

▪ **Acute Schizophrenia:**

- First-Rank Symptoms of Acute Schizophrenia (mnemonic: ABCD):
 - A → Auditory Hallucinations (2nd & 3rd person hallucinations)
 - B → Broadcasting of Thoughts:
 - Thought Insertion → alien thoughts are being inserted into one's mind.
 - Thought Withdrawal → thoughts are being "stolen" from one's mind.
 - Thought Broadcasting → thoughts are being broadcasted to others.
 - C → Controlled feelings, impulses, or acts.
 - D → Bizarre Delusions.

▪ **Chronic Schizophrenia:**

- Blunted (flattened) affect.
- Avolition → apathy & loss of drive
- Autism → social isolation & withdrawal
- Alogia → poverty of speech
- Poor self-care
- Catatonia → adopting awkward postures for prolonged periods.

(iii). Treatment:

- First episode of acute attack requires hospital admission.
- Subsequent acute relapses & chronic schizophrenia are treated on outpatient basis.
- Treatment → Anti-psychotic Medications:
 - These agents block D2 dopamine receptors in the brain.
 - These agents take about 2 – 4 weeks to act.
 - Types:
 - 1st Generation = Chlorpromazine, Haloperidol
 - 2nd Generation = Olanzapine, Clozapine, Risperidone

- Duration of treatment:
 - 1st episode of schizophrenia = 1-2 years (to prevent relapse)
 - Subsequent attacks = longer duration
- Side-Effects:
 - **Dopamine-Blocking Side-Effects:**
 - Akathasia – motor restlessness
 - Tardive dyskinesia
 - Parkinsonism
 - Galactorrhea, Gynecomastia
 - **Cholinergic-Blocking Side-Effects:**
 - Constipation, Urinary retention
 - Dry mouth
 - Impotence
 - Blurred vision
 - **Clozapine:**
 - Agranulocytosis (1%)
 - Requires WBC monitoring, initially weekly, then fortnightly, then monthly.
 - **CVS Side-Effects:**
 - Prolongation of QTc interval which predispose to:
 - VT, torsades de pointes, and sudden death.
- **Prognosis:**
 - Patient who develop acute schizophrenia:
 - 1/3rd have good outcome
 - 1/3rd develop chronic, incapacitating disease
 - 1/3rd develop relapsing disease



Clinical Pearl:

Neuroleptic Malignant Syndrome:

- It is a rare, but serious complication of anti-psychotic medication.
- It is characterized by fever, tremor, rigidity, and autonomic instability.
- It is characterized by elevated creatinine phosphokinase (CPK) and WBC.
- Treatment:
 - Stop antipsychotic medications.
 - Admit to ICU
 - Adequate hydration and reduce hyperthermia
 - Dantrolene and Bromocriptine
 - Mortality is 20% without treatment and 5% with treatment.



Clinical Pearl:

Schizophrenia & Related Disorders:

- **Schizophreniform Disorder** = All criteria for schizophrenia is met, but duration is < 6 months.
- **Schizoaffective Disorder** = All criteria for schizophrenia is met, but with prominent mood component i.e. either with manic episodes or severe depressive component.

Mood Disorders

- **Unipolar Depression** → episodes of depressed mood & associated symptoms.
- **Bipolar Depression** → episodes of elevated mood interspersed with episodes of depressed mood
- **Dysthymia** → chronic low-grade depressed mood without sufficient symptoms to be considered as major depression

I. Major Depressive Disorder:

- It is a mood (affective) disorder.
- It has prevalence of 5% in general population.
- Risk Factors:
 - Genetic predisposition
 - Chronic illnesses & stressful life events
 - Female > Male (2: 1)
 - Hypofunction of monoamine neurotransmitters – Serotonin & Norepinephrine
 - Hypothalamic-Pituitary-Adrenal (HPA) axis abnormalities.

(i). Diagnosis:

- It is diagnosed when patient has depressed mood + **≥ 5 signs & symptoms** (SIG E CAPS) that is present at **least 2-weeks**.
(Mnemonic: **SIG-E-CAPS**)
 - **S**leep = Increased (during day), Decreased (during night)
 - **I**nterest = Loss of interest in pleasurable activities (anhedonia)
 - **G**uilt = Feeling of worthlessness
 - **E**nergy = Lack of energy
 - **C**oncentration = Loss of concentration
 - **A**ppetite = Increased, OR, Decreased
 - **P**sychomotor = Agitation (anxiety), OR, Retardation (lethargy)
 - **S**uicide = Suicidal Ideation

(ii).

R_x

Treatment:

- Cognitive behavioral therapy & Interpersonal therapy
- Pharmacologic Therapy:
 - It effective in 50 – 75% of cases, but takes 2 – 6 weeks to take effect.
 - It should be taken for ≥ 6 months to prevent relapse.
 - Psychotherapy + Pharmacologic therapy is superior to either treatment alone.

<u>Class of Drugs</u>	<u>Side-Effects</u>
<u>Tricyclic Anti-Depressants (TCA):</u> <ul style="list-style-type: none"> Blocks re-uptake of serotonin & NE at synaptic cleft. Agents: Amitriptyline, Imipramine 	Postural hypotension Cardiotoxic – prolongs QRS Anti-Cholinergic: <ul style="list-style-type: none"> Dry Mouth Constipation Urinary Retention Sedation
<u>Selective Serotonin Reuptake Inhibitors (SSRIs):</u> <ul style="list-style-type: none"> It blocks reuptake of serotonin at synaptic cleft. It is less cardiotoxic & sedative than TCAs. Agents: Sertraline, Fluoxetine, Citalopram, Escitalopram 	Sexual side-effects Agitation Insomnia <u>"Serotonin Syndrome":</u> <ul style="list-style-type: none"> It occurs if used with MAOIs. It is characterized by fever, myoclonus, altered mental status, hemodynamic instability
<u>Monoamine Oxidase Inhibitors (MAOIs):</u> <ul style="list-style-type: none"> It inhibits metabolism of serotonin & NE and thus increases its availability in the synaptic cleft. Agents: Phenelzine, Tranylcypromine 	Orthostatic hypotension Weight gain <u>"Hypertensive crises"</u> – if taken with high-tyramine containing foods (cheese & red wine)
<u>Atypical Anti-Depressants:</u> <ul style="list-style-type: none"> Bupropion Mirtazapine Venlafaxine Trazodone 	Lowers seizure threshold. Weight gain, Sedation Diastolic hypertension Priapism, Sedation

II. Bipolar Disorder:

- It is mood disorder characterized by periods of mania, hypomania, and major depression.
 - Bipolar – I → Manic episodes + episodes of hypomania & major depression
 - Bipolar – II → at least 1 hypomanic episode + at least 1 major depression + NO mania
- Risk Factors & Epidemiology:
 - It equally affects men & women
 - It has prevalence of 1 – 2 %.
 - Risk Factors:
 - Genetic predisposition – (psychiatric disease with greatest genetic linkage)
 - High socioeconomic status

(i). Diagnosis:

- Symptoms of elevated mood for at least 1-week with impairment of daily level of functioning with ≥ 3 of following symptoms:

(Mnemonic: **DIG FAST**)

- Distractibility (attention easily drawn to unimportant & irrelevant external stimuli)
- Irrresponsibility & erratic uninhibited behavior
- Grandiosity (inflated self-esteem)
- Flight of Ideas
- Activity increased with increased libido
- Sleep is decreased
- Talkativeness with pressured speech
- Hypomanic Symptoms:

- These are similar to mania but are less severe to cause marked impairment of social & occupational functioning or requiring hospitalization.

(ii).

R_x

Treatment:

- Depression symptoms → anti-depressants + mood stabilizers
- Manic symptoms → mood stabilizers, anti-psychotics, valproate, lamotrigine
- Acute mania → lithium
- Mood Stabilizing Agents:
 - Anticonvulsants → valproate, lamotrigine
 - Anti-psychotics → olanzapine, risperidone
 - Lithium
 - It is the drug of first choice for mania.
 - It has narrow therapeutic window.
 - It requires regular blood level measurements to keep it 0.5 – 1 mmol/L.
 - Always check TSH & renal function prior to start and regularly thereafter.
 - Side-Effects:
 - Seizures
 - Tremors
 - Weight gain
 - **Hypothyroidism**
 - **Nephrogenic diabetes insipidus**
 - Increased Ca & PTH
 - Renal failure
 - Teratogenic (should not prescribed in 1st trimester of pregnancy)

(iii). Prognosis:

- Lifetime risk of suicide is 5 – 10%.
- It has high risk of relapse:
 - Relapse after 1 episode = 10 – 15%
 - Relapse after ≥ 3 episodes = 20 – 30%

Anxiety Disorders

I. Generalized Anxiety Disorder:

- It is a chronic anxiety state associated with uncontrollable anxiety that leads to significant functional impairment.
- **Clinical Features:**
 - It affects women > men (2:1).
 - Anxiety is present on most days ≥ 6 months
 - Associated somatic symptoms (≥ 3 symptoms):
 - Restlessness, Fatigue
 - Muscle tension
 - Disturbed sleep
 - Disturbed bowel habits
- **Treatment:**
 - Patient education, Lifestyle changes
 - Psychotherapy, Cognitive Behavior Therapy (CBT)
 - Pharmacotherapy:
 - Anti-depressants – agents of first choice:
 - Anti-depressants are given at a higher dose than that for depression.
 - Anti-depressants can worsen anxiety symptoms in the first 2-weeks.
 - Preferred agents:
 - SSRIs \rightarrow paroxetine
 - TCAs \rightarrow clomipramine
 - Beta-blockers (propranolol) for somatic symptoms.
 - Benzodiazepines:
 - These are useful for short-term treatment
 - These have high dependence – especially when given > 3 doses/week

II. Phobic Anxiety Disorder:

- It is an excessive & abnormal fear and avoidance of specific objects or situations.
- It is of two types:
 - **Social Phobia:**
 - It is fear of humiliation & embarrassment in social situations.
 - Examples: "stage fright", urinating in public restrooms.

○ Specific Phobia:

- It is fear & avoidance of an object or situation.
- Examples: fear of animals (spiders, lizards), fear of situations (height)

▪ Treatment:

- Patient education, Lifestyle changes
- Psychotherapy, Cognitive Behavior Therapy (CBT)
- **"Desensitization"** – i.e. graded exposure of the feared objects or situations.
- Pharmacotherapy:
 - **Anti-depressants – agents of first choice**
 - Benzodiazepines
 - Beta-blockers – for performance anxiety & stage fright

III. Panic Anxiety Disorder:

- It is characterized by recurrent panic attacks, which are episodes of extreme anxiety, often with marked physical symptoms.
- It is more common in women.
- It has acute onset with ≥ 4 somatic symptoms that peak within 10 minutes.
 - Tachycardia
 - Hyperventilation
 - Sweating
 - Dizziness
 - Chest pain
 - Fear of dying – (fear of impending doom).
 - **"Agoraphobia"**:
 - It is the fear & avoidance of places from which escape would be difficult in the event of panic symptoms.
- Treatment:
 - Patient education, CBT
 - Desensitization
 - Pharmacotherapy → SSRIs, TCAs

	<u>Generalized Anxiety Disorder</u>	<u>Phobic Anxiety Disorder</u>	<u>Panic Disorder</u>
<u>Onset</u>	Persistent	Situational	Paroxysmal
<u>Behavior</u>	Agitation	Avoidance	Escape
<u>Cognition</u>	Worry	Fear of situation	Fear if symptom
<u>Symptoms</u>	Persistent	On exposure	Episodic

Stress-related Disorders

I. ASD & PTSD:

- ASD = acute stress disorder
- PTSD = post-traumatic stress disorder
- These are characterized by severe anxiety symptoms and follow a major stressful event.
- ASD is diagnosed when:
 - The symptoms last **> 2 days, but < 1-month**
 - The onset of symptoms is within 1-month of stressful event.
- PTSD is diagnosed when:
 - The symptoms last **> 1 month.**
 - The onset of symptoms can be within days to months.
- **Clinical Features:**
 - It can occur at any age.
 - **"Flashbacks"** – recurrent intrusive memories of the traumatic event.
 - **"Autonomic Arousal"** – palpitations, anxiety, enhanced startle
 - **"Sleep disturbance"** – nightmares about the traumatic event.
- **Treatment**
 - ASD → support, direct advice and support for emotional catharsis
 - PTSD → CBT, eye movement de-sensitization and re-processing (EMDR)
 - Pharmacotherapy:
 - Benzodiazepines can reduce arousal in ASD.
 - Anti-depressants are moderately successful in PTSD.

II. Adjustment Disorder:

- It is a prolonged emotional response to major stressor.
- It is more common, but less severe than ASD & PTSD
- **Clinical Features:**
 - Symptoms of depression and/or anxiety
 - **Symptoms develop within a month of the onset of the stress.**
 - Associated symptoms → anger, aggressive behavior, alcohol use.
 - Grief reactions following bereavement are a particular type of adjustment disorder.
- **Management:**
 - Supportive therapy
 - Benzodiazepines can aid sleep in adjustment disorder.

Somatoform & Factitious Disorders

I. Somatoform Disorders:

- It is a group of psychiatric disorders characterized by:
 - Physical (somatic) symptoms that are not medically explained.
 - Patients have no conscious control over the symptoms.
 (If symptoms are consciously presented, it is factitious disorder).

▪ Clinical Features:

(i). Somatoform Autonomic Dysfunction:

- It consists of somatic symptoms referable to bodily organs that are largely under the control of the autonomic nervous system.
 - Cardiovascular → cardiac neurosis
 - Respiratory → psychogenic hyperventilation
 - Gastrointestinal → psychogenic vomiting, irritable bowel syndrome
- Treatment = anti-depressants, CBT

(ii). Somatoform Pain Disorder:

- It consists of severe, persistent pain not adequately explained by a medical condition.
- Treatment:
 - Antidepressant drugs → TCAs, SSRI (duloxetine)
 - Anticonvulsants → carbamazepine, gabapentin and pregabalin.
 - CBT and multidisciplinary pain management teams are also useful.

(iii). Chronic Fatigue Syndrome (CFS):

- It is characterized by excessive fatigue after minimal physical or mental exertion, poor concentration, dizziness, muscular aches and sleep disturbance.
- It mimics viral infection such as infectious mononucleosis, influenza or hepatitis.
- Treatment:
 - Graded-exercise and with CBT
 - Antidepressant drugs → TCAs, SSRI
 - Anticonvulsants → gabapentin and pregabalin.

(iv). Conversion Disorder:

- It is characterized by a loss or distortion of ≥ 1 neurologic functions that is not fully explained by organic disease.
- Its etiology is unknown but is associated with recent stress and with adverse childhood experiences, including physical and sexual abuse.
 - Sensory System → anesthesia, paresthesia, dissociative blindness

- Motor System → gait disorder, weakness, ticks, tremors,
- Seizure System → pseudo-seizures
- Memory → dissociative amnesia
- Primary Gain → keeps internal conflicts outside patient's awareness
- Secondary Gain → benefits received from being "sick".
- "La belle indifference" → patient seems unconcerned about impairment

- Treatment = CBT, Psychotherapy

(v). Somatization Disorder:

- Also known as "Briquet's syndrome".
- It is characterized by multiple medically unexplained physical symptoms affecting several bodily systems.
- Clinical Features:
 - It is more common in women.
 - Long & complicated medical histories.
 - Multitude of negative investigations
 - Unhelpful operations, particularly hysterectomy and cholecystectomy.
- Treatment:
 - There is no proven treatment.
 - Patient should have a single identified physician as the primary caretaker – to ensure that unnecessary investigations and surgical procedures are avoided.

(vi). Hypochondrial Disorder:

- It is characterized by a strong fear or belief that one has a serious, often fatal, disease (such as cancer), and that fear persists despite appropriate medical reassurance.
- It can progress to reach delusional intensity.
- Treatment:
 - CBT
 - Anti-psychotics for those who suffer delusions.

(vii). Body Dysmorphic Disorder:

- It is characterized by the belief that one is disfigured in some way.
- Clinical Features:
 - It is more common in women.
 - Most common concerns involve facial flaws.
 - Attempt to hide the alleged deformity
 - Constant mirror-checking
 - Inappropriate requests for cosmetic surgery
 - Causes impairment in level of functioning

- Associations → anxiety, depression, family history of psychiatric disorders
- Treatment = CBT, anti-depressants

II. Factitious Disorder:

- It is a disorder characterized by the conscious production of signs and symptoms of both medical and mental disorders.
- **Clinical Features:**
 - The primary goal is to assume the sick role and eventually hospitalization.
 - It is common in women and health-care workers.
 - They typically demand treatment when in the hospital.
 - If test results return negative, they tend to accuse doctors and threaten litigation.
 - They become angry when confronted
 - **Munchausen's syndrome:**
 - It severe and chronic form of factitious disorder.
 - The patient visits different hospitals for the same complaint and persuade doctors to run tests, initiate treatment, even surgery.
 - **Munchausen's syndrome by Proxy:**
 - It is a type of factitious disorder in which the "caregiver" makes someone else ill and enjoys taking on the role of concerned onlooker.
- **Treatment:**
 - Management is by gentle but firm confrontation with clear evidence of the fabrication of illness, together with an offer of psychological support.
 - Treatment is usually declined but recognition of the condition may help to avoid further iatrogenic harm.



Clinical Pearl:

Medically Unexplained Symptoms (MUS):

- Patient NOT consciously controlling the signs & symptoms → somatoform disorder
- Patient consciously controlling the signs & symptoms:
 - Identifiable gain → NO = factitious disorder
 - Identifiable gain → YES = malingering
- In factitious disorder the primary gain is to assume "sick" role.
- In malingering the primary gain is obvious – money, avoidance of work, etc.
- Malingering is not a mental disorder.

Eating Disorders

I. Anorexia Nervosa:

- It is an eating disorder characterized by failure to maintain a normal body weight, fear and preoccupation with gaining weight and unrealistic self-evaluation as overweight.
- **Diagnostic Criteria:**
 - Weight loss of at 15% of total body weight or BMI < 17.5 mg/kg²
 - Avoidance of high calorie foods
 - Amenorrhea for at least 3 months
 - Distortion of body image so that patient regard themselves as fat even when severely underweight
- **Clinical Features:**
 - It is more common in women (90%).
 - Age of onset = 15 – 19 years, late-onset is associated with poor prognosis.
 - Marked weight loss, arising from food avoidance
 - Associated with bingeing, purging, excessive exercise, use of diuretics and laxatives.
 - Anxiety and depressive symptoms are common accompaniments.
 - Downy hair (“lanugo”) may develop on the back, forearms and cheeks.
 - All organ systems may be affected:
 - Cardiac → Arrhythmias (sinus bradycardia, VT), ECG abnormalities
 - Hematologic → anemia, thrombocytopenia, leukopenia
 - Endocrine → amenorrhea, sick euthyroid state, delayed puberty
 - Gastrointestinal → abnormal LFTs, constipation
 - Metabolic:
 - Uremia, renal calculi
 - Metabolic alkalosis, hypochloremia, hypokalemia – from emesis.
- **Management:**
 - Family behavior therapy (FBT) has efficacy among adolescent but not adult patients.
 - There is limited evidence for effectiveness of CBT.
 - Psychotropic drugs are of no proven benefit in AN.
 - Antidepressants can be given if associated with depressive disorder.
 - Hospitalization → suicidal, risk of death from systemic complications

- Compulsory admission and refeeding (including tube feeding) are very occasionally resorted to when patients are at risk of death and other measures have failed.

II. Bulimia Nervosa:

- It is an eating disorder characterized by frequent binge-eating and a self-image that is unduly influenced by weight.
- It is of two types:
 - Bulimia Nervosa → binge-eating and purging behavior
 - Binge-eating Disorder → binge-eating but no purging behavior
- **Diagnostic Criteria:**
 - Recurrent bouts of binge eating
 - Lack of self-control over eating during binges
 - Self-induced vomiting, purging, or dieting after bingeing
 - Weight maintained within normal limits.
- **Clinical Features:**
 - It is more common in women (90%).
 - The body weight is normal – unlike anorexia nervosa.
 - There is morbid fear of fatness with disordered eating behavior.
 - Signs of Self-induced Vomiting:
 - “Pitted Enamel” → erosion of dental enamel from gastric acid.
 - “Russel Sign” → Scarring of knuckles from self-induced gagging & vomiting.
 - Electrolyte disturbance → hypokalemia can cause cardiac arrhythmias
- **Management:**
 - CBT – achieves both short-term & long-term improvement.
 - Interpersonal therapy
 - Anti-depressants – fluoxetine is the agent of choice.

GLOSSARY

A:

Abdominal aortic aneurysm (chapter 5)
 Acanthosis nigricans (chapter 14)
 Acetaminophen poisoning (Chapter 1)
 Achalasia (chapter 9)
 Acromegaly (chapter 7)
 Acute cholecystitis (chapter 10)
 Acute coronary syndrome (chapter 5)
 Acute interstitial nephritis (chapter 4)
 Acute kidney injury (chapter 4)
 Acute liver failure (chapter 10)
 Acute lymphocytic leukemia (chapter 11)
 Acute myelogenous leukemia (chapter 11)
 Acute pancreatitis (chapter 9)
 Acute pulmonary edema (chapter 5)
 Acute renal failure (chapter 4)
 Acute tubular necrosis (chapter 4)
 Addison's disease (chapter 7)
 Adrenal insufficiency (chapter 7)
 Adrenogenital syndrome (chapter 7)
 AIDS (Chapter 2)
 Alcoholic hepatitis (chapter 10)
 Allergic bronchopulmonary aspergillosis (chapter 6)
 Alpha1-antitrypsin deficiency (chapter 10)
 Alport syndrome (chapter 4)
 Alzheimer's disease (chapter 13)
 Amiodarone (chapter 7)
 Amoebiasis (chapter 2)
 Amoebic liver abscess (chapter 2)
 Anemia (chapter 11)
 Anemia of chronic disease (chapter 11)
 Anion gap (Chapter 3)

Ankylosing spondylitis (chapter 12)
 Aortic dissection (chapter 5)
 Aortic regurgitation (chapter 5)
 Aortic stenosis (chapter 5)
 Aplastic anemia (chapter 11)
 Argyll-Robertson pupils (chapter 13)
 Asbestosis (chapter 6)
 Ascites (chapter 10)
 Aspergilloma (chapter 6)
 Aspirin (Chapter 1)
 Asthma (chapter 6)
 Asystole (chapter 5)
 Atrial fibrillation (chapter 5)
 Atrial flutter (chapter 5)
 Autoimmune hemolytic anemia (chapter 11)
 Autoimmune hepatitis (chapter 10)

B:

Bacterial overgrowth syndrome (chapter 9)
 Barrett esophagus (chapter 9)
 Basal cell carcinoma (chapter 14)
 Behcet's syndrome (chapter 12)
 Bell's palsy (chapter 13)
 Benign intracranial hypertension (chapter 13)
 Benign prostatic hyperplasia (chapter 4)
 Benzodiazepines (Chapter 1)
 Brain abscess (chapter 13)
 Brain natriuretic peptide (chapter 5)
 Bronchiectasis (chapter 6)
 Bronchogenic cancer (chapter 6)
 Budd-Chiari syndrome (chapter 10)
 Buerger disease (chapter 12)

C:

Cannabis (Chapter 1)
 Carbon monoxide poisoning (Chapter 1)
 Cardiomyopathy (chapter 5)

Carpal tunnel syndrome (chapter 13)
 Celiac disease (chapter 9)
 Central Pontine Myelinolysis (Chapter 3)
 Chancroid (Chapter 2)
 Child – Pugh classification (chapter 10)
 Chlamydia (Chapter 2)
 Cholangiocarcinoma (chapter 10)
 Cholelithiasis (chapter 10)
 Chronic kidney disease (chapter 4)
 Chronic lymphocytic leukemia (chapter 11)
 Chronic myeloid leukemia (chapter 11)
 Chronic pancreatitis (chapter 9)
 Churg-Strauss Syndrome (chapter 12)
 Cirrhosis (chapter 10)
 Clostridium difficile (Chapter 2)
 Cluster headache (chapter 13)
 Cocaine (Chapter 1)
 Colonic adenocarcinoma (chapter 9)
 Complete heart block (chapter 5)
 Congenital adrenal hyperplasia (chapter 7)
 Congestive heart failure (chapter 5)
 Constrictive pericarditis (chapter 5)
 COPD (chapter 6)
 Chronic obstructive pulmonary disease (chapter 6)
 Craniopharyngioma (chapter 7)
 Crigler-Najjar Syndrome (chapter 10)
 Crohn's disease (chapter 9)
 Cryoglobulinemia (chapter 12)
 Cryptococcal meningitis (Chapter 2)
 Cushing syndrome (chapter 7)
 Cystic fibrosis (chapter 6)

D:

De Quervain thyroiditis (chapter 7)
 Dengue (Chapter 2)
 Dermatitis (chapter 14)
 Dermatitis herpetiformis (chapter 14)
 Dermatomyositis (chapter 12)
 Diabetes insipidus (chapter 7)
 Diabetes mellitus (chapter 8)
 Diabetic ketoacidosis (chapter 8)
 Diabetic nephropathy (chapter 8)

Diabetic neuropathy (chapter 8)
 Diabetic retinopathy (chapter 8)
 Dialysis (chapter 4)
 Diffuse esophageal spasm (chapter 9)
 Diffuse parenchymal lung disease (chapter 6)
 Disseminated intravascular coagulation (chapter 11)
 Diverticulitis (chapter 9)
 Diverticulosis (chapter 9)
 Dysphagia (chapter 9)

E:

Eczema (chapter 14)
 Encephalitis (chapter 13)
 Epilepsy (chapter 13)
 Erythema infectiosum (Chapter 2)
 Erythema multiforme (chapter 14)
 Erythema nodosum (chapter 14)
 Esophageal cancer (chapter 9)
 Esophageal varices (chapter 10)
 Essential thrombocythemia (chapter 11)
 Ethylene glycol (Chapter 1)
 Exanthem Sabitum (Chapter 2)

F:

Factitious thyroiditis (chapter 7)
 Familial adenomatous polyposis (chapter 9)
 Fibromyalgia (chapter 12)
 First-degree AV block (chapter 5)
 Flapping tremor (chapter 13)
 Focal segmental glomerulosclerosis (chapter 4)
 Folate deficiency anemia (chapter 11)
 Friedreich's ataxia (chapter 13)

G:

Gastric cancer (chapter 9)
 Gastric lymphoma (chapter 9)
 Gastrinoma (chapter 9)
 Gastritis (chapter 9)
 Gastroesophageal reflux disease (chapter 9)
 Giant cell arteritis (chapter 12)
 Giardiasis (chapter 2)
 Gigantism (chapter 7)

Gilbert syndrome (chapter 10)
 Glomerulonephritis (chapter 4)
 Glucose-6-phosphate dehydrogenase deficiency (chapter 11)
 Gonorrhea (Chapter 2)
 Goodpasture's syndrome (chapter 4)
 Gout (chapter 12)
 Granuloma Inguinale (Chapter 2)
 Graves' disease (chapter 7)
 Growth hormone adenoma (chapter 7)
 Guillian Barre syndrome (chapter 13)

H:

Hemochromatosis (chapter 10)
 Hemodialysis (chapter 4)
 Hemofiltration (chapter 4)
 Hemophilia (chapter 11)
 Henoch-Schonlein purpura (chapter 12)
 Heparin-induced thrombocytopenia (chapter 11)
 Hepatic encephalopathy (chapter 10)
 Hepatocellular carcinoma (chapter 10)
 Hepato-pulmonary syndrome (chapter 10)
 Hepato-renal syndrome (chapter 10)
 Hereditary non-polyposis colorectal cancer (chapter 9)
 Hereditary spherocytosis (chapter 11)
 Hiatal hernia (chapter 9)
 Hirschprung's disease (chapter 9)
 Hodgkin's lymphoma (chapter 11)
 Human immunodeficiency virus (Chapter 2)
 Human papilloma virus (Chapter 2)
 Huntington's disease (chapter 13)
 Hydatid liver disease (chapter 2)
 Hyperaldosteronism (chapter 7)
 Hypercalcemia (chapter 7)
 Hyperkalemia (Chapter 3)
 Hypermagnesemia (Chapter 3)
 Hypernatremia (Chapter 3)
 Hyperosmolar Nonketotic Coma (HONK) (chapter 8)
 Hyperparathyroidism (chapter 7)
 Hypersensitivity pneumonitis (chapter 6)

Hypertension (chapter 5)
 Hypertensive emergency (chapter 5)
 Hypertensive urgency (chapter 5)
 Hyperthyroidism (chapter 7)
 Hypertrophic pulmonary Osteoarthropathy (chapter 6)
 Hypocalcemia (chapter 7)
 Hypokalemia (Chapter 3)
 Hypomagnesemia (Chapter 3)
 Hyponatremia (Chapter 3)
 Hypoparathyroidism (chapter 7)
 Hypopituitarism (chapter 7)
 Hypothyroidism (chapter 7)

I:

Idiopathic pulmonary fibrosis (chapter 6)
 Idiopathic thrombocytopenic purpura (chapter 11)
 IgA nephropathy (chapter 4)
 Infectious esophagitis (chapter 9)
 Infectious mononucleosis (Chapter 2)
 Infective endocarditis (chapter 5)
 Inflammatory bowel disease (chapter 9)
 Insulinoma (chapter 9)
 Iron deficiency anemia (chapter 11)
 Iron toxicity (Chapter 1)
 Irritable bowel syndrome (chapter 9)

J:

Jaundice (chapter 10)

K:

Kala - Azar (chapter 2)
 Kaposi's sarcoma (Chapter 2)
 Kawasaki disease (chapter 12)
 Klinefelter syndrome (chapter 7)

L:

Lactose intolerance (chapter 9)
 Lambert-Eaton myasthenic syndrome (chapter 13)
 Left axis deviation (chapter 5)

Left bundle branch block (LBBB) (chapter 5)
 Leprosy (Chapter 2)
 Lithium toxicity (Chapter 1)
 Lower GI bleeding (chapter 9)
 Lumbar disc herniation (chapter 13)
 Lung cancer (chapter 6)
 Lymphogranuloma venereum (Chapter 2)

M:

Measles (Chapter 2)
 Meckel diverticulum (chapter 9)
 Membranoproliferative GN (chapter 4)
 Membranous glomerulonephritis (chapter 4)
 Menetrier disease (chapter 9)
 Meningitis (chapter 13)
 Metabolic acidosis (Chapter 3)
 Metabolic alkalosis (Chapter 3)
 Methanol poisoning (Chapter 1)
 Microscopic polyangiitis (chapter 12)
 Migraine (chapter 13)
 Minimal change disease (chapter 4)
 Mitral regurgitation (chapter 5)
 Mitral stenosis (chapter 5)
 Mitral valve prolapse (chapter 5)
 Mixed connective tissue disease (chapter 12)
 Motor neuron disease (chapter 13)
 Multiple endocrine neoplasia (chapter 7)
 Multiple myeloma (chapter 11)
 Multiple myeloma (chapter 14)
 Multiple sclerosis (chapter 13)
 Mumps (Chapter 2)
 Myasthenia gravis (chapter 13)
 Mycobacterium Avium Intracellulare (Chapter 2)
 Myocardial infarction (chapter 5)
 Myxedema coma (chapter 7)

N:

Narcolepsy (chapter 13)
 Nephritic syndrome (chapter 4)
 Nephrolithiasis (chapter 4)
 Nephrotic syndrome (chapter 4)
 Neurosyphilis (chapter 13)

Non-alcoholic fatty liver disease (chapter 10)
 Non-Hodgkin's lymphoma (chapter 11)
 Normal pressure hydrocephalus (chapter 13)

O:

Opioids (Chapter 1)
 Organophosphate poisoning (Chapter 1)
 Osteoarthritis (chapter 12)
 Osteomalacia (chapter 12)
 Osteomyelitis (chapter 12)

P:

Paget's disease (chapter 12)
 Pancoast syndrome (chapter 6)
 Pancreatic cancer (chapter 9)
 Pancreatic pseudocyst (chapter 9)
 Paracetamol poisoning (Chapter 1)
 Parkinson's disease (chapter 13)
 Paroxysmal nocturnal hemoglobinuria (chapter 11)
 Pemphigoid (chapter 14)
 Pemphigus vulgaris (chapter 14)
 Peptic ulcer disease (chapter 9)
 Pericardial effusion (chapter 5)
 Pericarditis (chapter 5)
 Peritoneal dialysis (chapter 4)
 Pernicious anemia (chapter 11)
 Pharyngeal pouch (chapter 9)
 Pheochromocytoma (chapter 7)
 Pick's disease (chapter 13)
 Pneumoconiosis (chapter 6)
 Pneumocystis Jirovecii Pneumonia (Chapter 2)
 Pneumonia (chapter 6)
 Polyarteritis nodosa (chapter 12)
 Polycystic ovarian syndrome (chapter 7)
 Polycythemia rubra vera (chapter 11)
 Polymyalgia rheumatica (chapter 12)
 Polymyositis (chapter 12)
 Portal hypertension (chapter 10)
 Post-streptococcal GN (chapter 4)
 Primary biliary cirrhosis (chapter 10)
 Primary myelofibrosis (chapter 11)
 Primary sclerosing cholangitis (chapter 10)

Prinzmetal's angina (chapter 5)
 Progressive multifocal
 leukoencephalopathy (chapter 13)
 Prolactinoma (chapter 7)
 Prostatic adenocarcinoma (chapter 4)
 Pseudogout (chapter 12)
 Pseudotumor Cerebri (chapter 13)
 Psoriasis (chapter 14)
 Psoriatic arthropathy (chapter 12)
 Pulmonary embolism (chapter 6)
 Pulmonary function tests (chapter 6)
 Pyelonephritis (chapter 4)
 Pyoderma gangrenosum (chapter 14)
 Pyogenic liver abscess (chapter 2)

R:

Rabies (chapter 13)
 Reactive arthritis (chapter 12)
 Renal amyloidosis (chapter 4)
 Renal replacement therapy (chapter 4)
 Renal tubular acidosis (chapter 4)
 Respiratory acidosis (Chapter 3)
 Respiratory alkalosis (Chapter 3)
 Restless leg syndrome (chapter 13)
 Rheumatic fever (chapter 5)
 Rheumatoid arthritis (chapter 12)
 Rickets (chapter 12)
 Right axis deviation (chapter 5)
 Right bundle branch block (RBBB) (chapter 5)
 Rubella (Chapter 2)

S:

Sarcoidosis (chapter 6)
 Scabies (chapter 14)
 Scalded skin syndrome (Chapter 2)
 Schilling test (chapter 11)
 Second-degree AV block (chapter 5)
 Septic arthritis (chapter 12)
 Sexually transmitted diseases (Chapter 2)
 Sheehan's syndrome (chapter 7)
 SIADH (Chapter 3)
 Sick Euthyroidism (chapter 7)
 Sickle cell disease (chapter 11)

Sideroblastic anemia (chapter 11)
 Silicosis (chapter 6)
 Sinus bradycardia (chapter 5)
 Sinus tachycardia (chapter 5)
 Sjogren's syndrome (chapter 12)
 Spinal cord compression (chapter 13)
 Spontaneous bacterial peritonitis (chapter 10)
 Squamous cell carcinoma (chapter 14)
 Stable angina (chapter 5)
 Status Epilepticus (chapter 13)
 Stevens-Johnson syndrome (chapter 14)
 Stroke (chapter 13)
 Subarachnoid hemorrhage (chapter 13)
 Supraventricular tachycardia (chapter 5)
 Syndrome of inappropriate ADH secretion (Chapter 3)
 Syphilis (Chapter 2)
 Systemic lupus erythematosus (chapter 12)
 Systemic sclerosis (chapter 12)

T:

Takayasu arteritis (chapter 12)
 Tension headache (chapter 13)
 Thalassemia (chapter 11)
 Thrombotic thrombocytopenic purpura (chapter 11)
 Thyroid cancer (chapter 7)
 Thyroid storm (chapter 7)
 Tinea versicolor (chapter 14)
 Torsades de pointes (chapter 5)
 Toxic epidermal Necrolysis (chapter 14)
 Toxic shock syndrome (Chapter 2)
 Toxoplasmosis (Chapter 2)
 Transverse myelitis (chapter 13)
 Tremors (chapter 13)
 Tricyclic antidepressants (Chapter 1)
 Trigeminal neuralgia (chapter 13)
 Tuberculosis (chapter 6)
 Turner syndrome (chapter 7)
 Typhoid (Chapter 2)

U:

- Ulcerative colitis (chapter 9)
- Unstable angina (chapter 5)
- Upper GI bleeding (chapter 9)
- Urinary tract calculi (chapter 4)
- Urinary tract infection (chapter 4)
- Urticaria (chapter 14)

V:

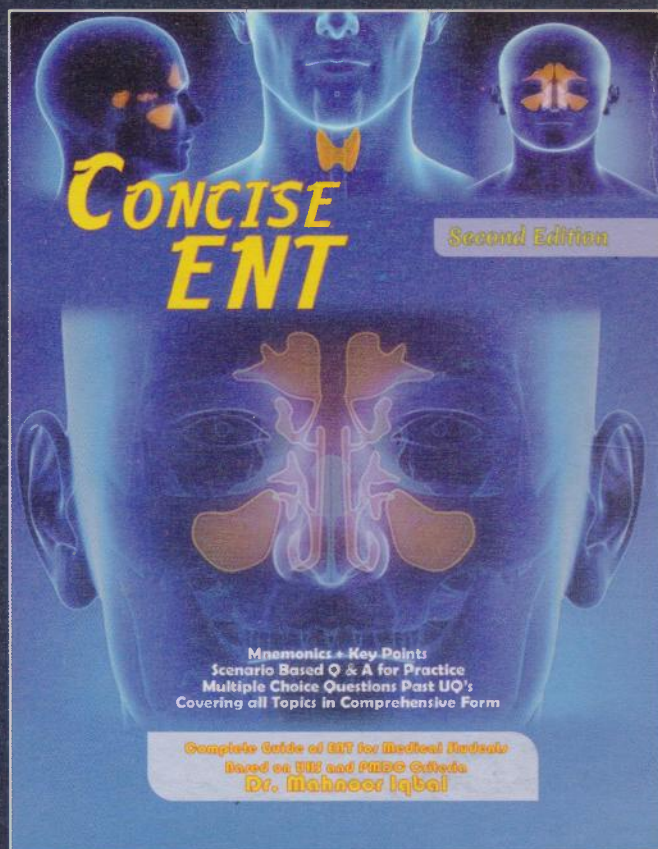
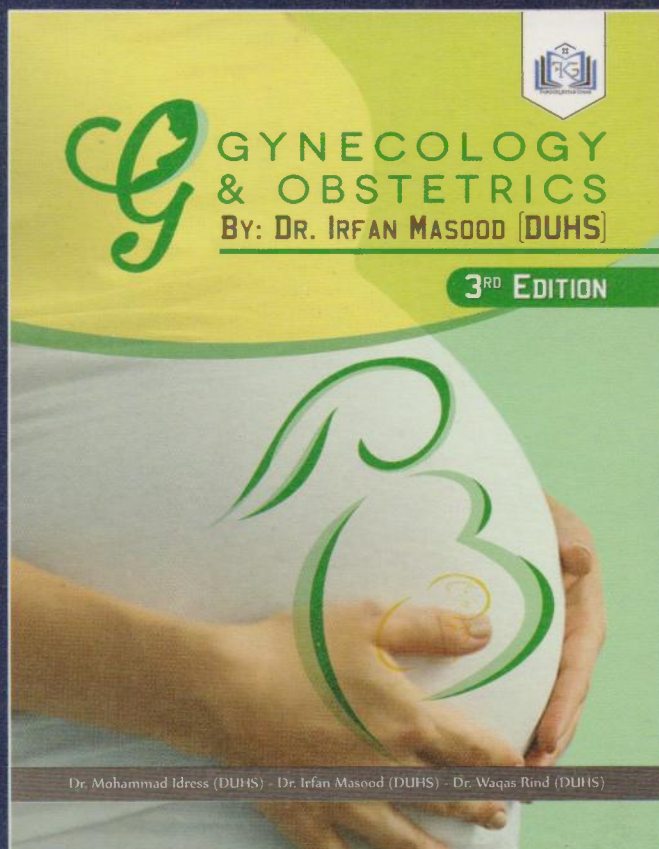
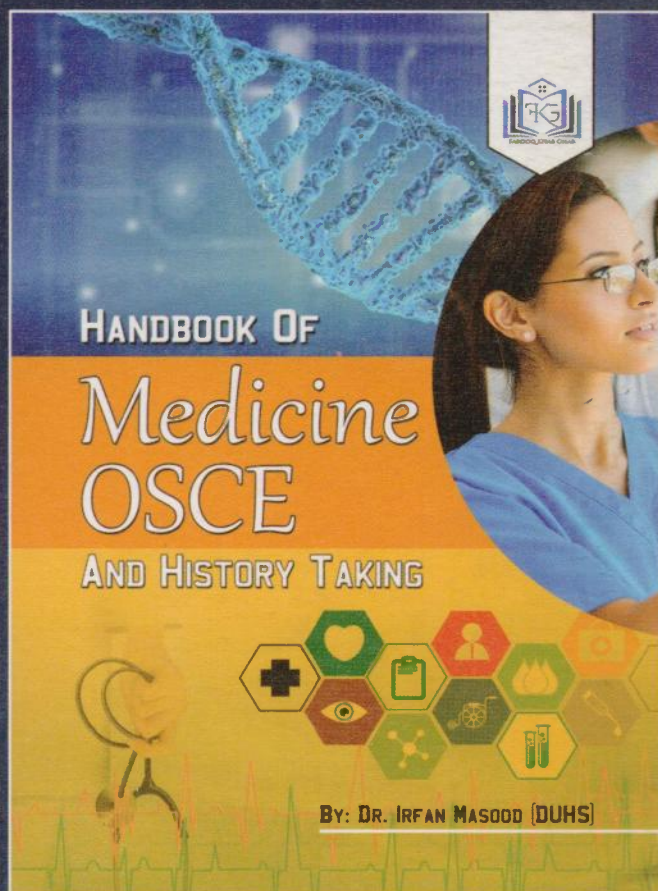
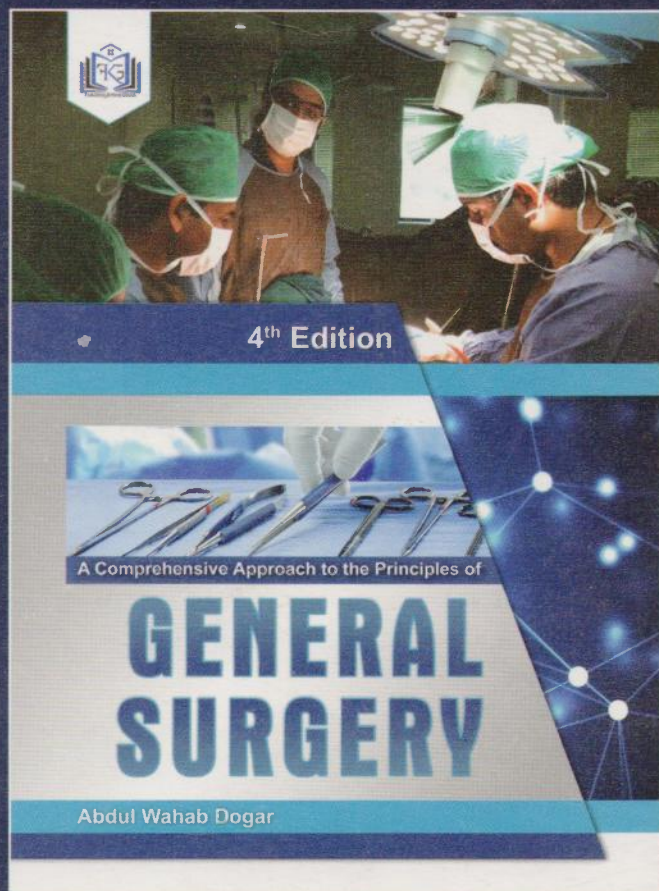
- Variant angina (chapter 5)
- Varicella-Zoster (Chapter 2)
- Vascular dementia (chapter 13)
- Veno-occlusive disease (chapter 10)
- Ventricular fibrillation (chapter 5)
- Ventricular tachycardia (chapter 5)
- Vitamin B12 deficiency anemia (chapter 11)
- Von Willebrand disease (chapter 11)

W:

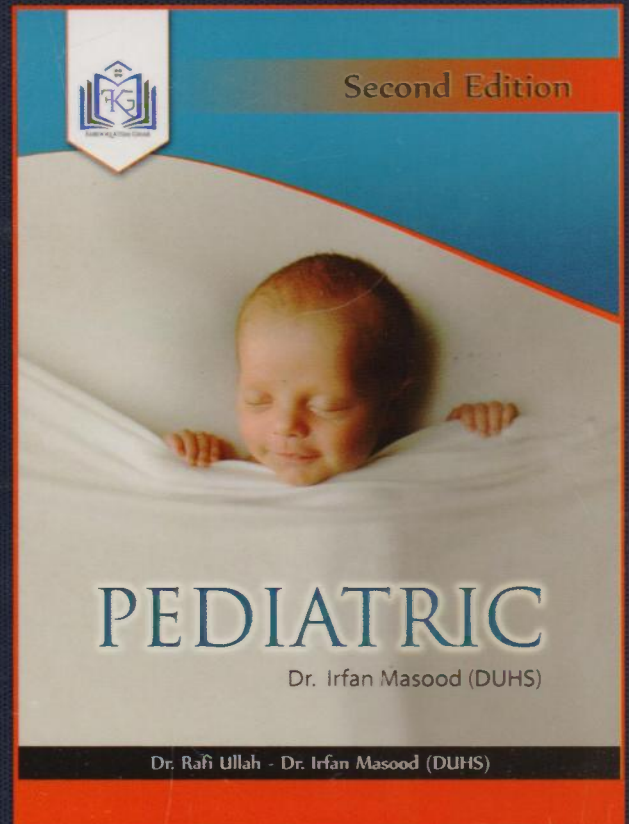
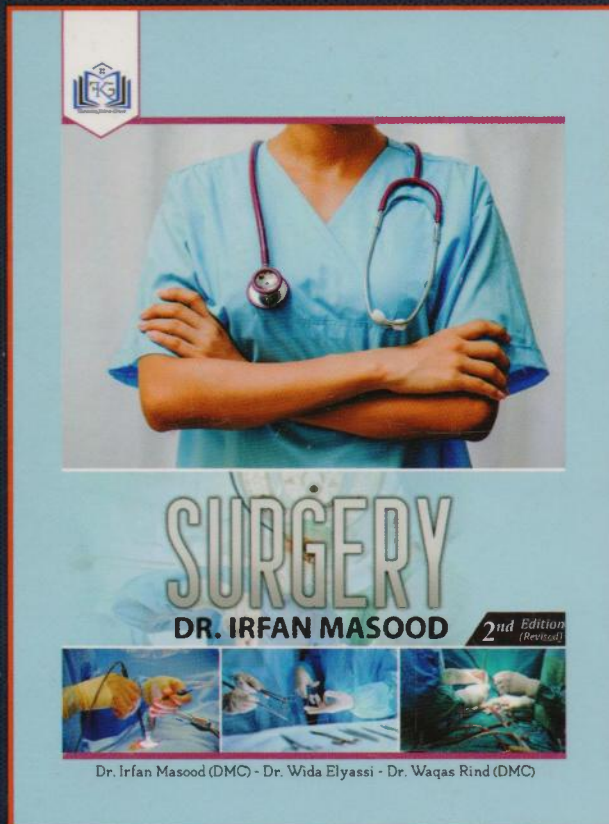
- Waldenstrom macroglobulinemia (chapter 11)
- Waterhouse-Friderichsen syndrome (chapter 7)
- Wegener's granulomatosis (chapter 12)
- Wegener's granulomatosis (chapter 4)
- Wernicke-Korsakoff disease (chapter 13)
- Whipple disease (chapter 9)
- Wilson's disease (chapter 10)
- Wolff-Parkinson White (WPW) syndrome (chapter 5)

Z:

- Zenker's diverticulum (chapter 9)
- Zollinger Ellison syndrome (chapter 9)



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